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VOLUME 155 • NUMBER 1 JULY 1991

ARTICLES

27 The Health Status of Minority Populations in the United States
H W NICKENS

33 Fine Needle Aspiration Biopsy of Superficial Masses in Children
L P HOWELL, L A RUSSELL, P H HOWARD, and R L TEPLITZ

39 Nonsteroidal Anti-inflammatory Drugs—Proposed Guidelines for Monitoring Toxicity
T M BUSH, T L SHLOTZHAUER, and K IMAI

43 Is Deleting the Digital Rectal Examination a Good Idea?
M A SUTTON, R P GIBBONS, and R J CORREA, Jr

CONFERENCES AND REVIEWS

47 The Clinical Diagnosis of Splenomegaly
J C YANG, L S RICKMAN, and S K BOSSER

53 Understanding Osteoporosis
R MARCUS

61 Painful Subacute Thyroiditis in Hawaii
R A NORDYKE, F I GILBERT, Jr, and C LEW

EPITOMES

64 Important Advances in Neurology

ALERTS, NOTICES, AND CASE REPORTS

72 Intravascular (Angiotropic) Large-cell Lymphoma ('Malignant Angioendotheliomatosis') With Small Vessel Pulmonary Vascular Obstruction and Hypercalcemia
J L CURTIS, M L WARNOCK, D J CONRAD, L K HELFEND, and H A BOUSHEY

76 Resolution of Bowel Obstruction Due to Newly Diagnosed Inoperable Advanced Ovarian Cancer With Medical Therapy
T P DRAKES

78 Intractable Hiccups as a Presentation of Central Nervous System Sarcoidosis
J P CONNOLLY, T J CRAIG, R M SANCHEZ, W S SAGEMAN, and R E OSBORN

COMMENTARY

80 The Trial and Tribulation of Egerton Yorrick Davis
G N BURROW

EDITORIALS

83 Subacute Thyroiditis • Two Medical Worlds—Separate and Unequal

CORRESPONDENCE

86 Redwood Medicare Assignment Program • Cancer Patients and Support Groups

LESSONS FROM THE PRACTICE

87 The Sailor Who Couldn't Play Pool
P L KINGSLEY

88 Concerned Patient
E VAN BRUNT

OTHER FEATURES

2 Instructions for Authors

14 Continuing Medical Education Activities in California, Hawaii, and Nevada; Colorado; Idaho; New Mexico; Utah; Washington; Wyoming

25 Subscription Information

94 Classified Advertising

106 Western State Medical Associations' Meetings

Poems: 38, 46, 82

Detailed Table of Contents: 6, 12, 16

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Hypersensitivity to minoxidil, propylene glycol, or ethanol.

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1. Need for normal scalp: Before starting treatment, make sure that the patient has a normal, healthy scalp. Local abrasion or dermatitis may increase absorption and hence the risk of side effects.

2. Potential adverse effects. Although extensive use of topical minoxidil has not revealed evidence that enough minoxidil is absorbed to have systemic effects, greater absorption because of misuse, individual variability, or unusual sensitivity could, at least theoretically, produce a systemic effect.

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- tachycardia
- increased incidence of angina or new onset of angina

Patients with underlying heart disease, including coronary artery disease and congestive heart failure, would be at particular risk of these potential effects. Additive effects could also emerge in patients being treated for hypertension.

Potential patients should have a history and physical and should be advised of potential risks. A risk/benefit decision should be made. Heart patients should realize that adverse effects may be especially serious.

Alert patients to the possibility of tachycardia and fluid retention and monitor for increased heart rate, weight gain, or other systemic effects.

PRECAUTIONS

General Precautions: Monitor patients 1 month after starting ROGAINE and at least every 6 months afterward. Discontinue ROGAINE if systemic effects occur.

The alcohol base will burn and irritate the eye. If ROGAINE reaches sensitive surfaces (eg, eye, abraded skin, and mucous membranes), bathe with copious cool water.

Avoid inhaling the spray.

Do not use in conjunction with other topical agents such as corticosteroids, retinoids and petrolatum, or agents that enhance percutaneous absorption.

ROGAINE is for topical use only. Each mL contains 20 mg minoxidil and accidental ingestion could cause adverse systemic effects.

Decreased integrity of the epidermal barrier caused by inflammation or disease of the skin, eg, excoriations, psoriasis, or severe sunburn, may increase minoxidil absorption.

Patient Information: A patient information leaflet is included with each package and in the full product information.

Drug Interactions: No drug interactions are known. Theoretically, absorbed minoxidil may potentiate orthostatic hypotension in patients taking guanethidine.

Carcinogenesis, Mutagenesis, and Impairment of Fertility. No carcinogenicity was found with topical application. Oral administration may be associated with an increased incidence of malignant lymphomas in female mice and hepatic nodules in male mice. In rats, there was a dose-dependent reduction in conception rate.

Pregnancy Category C: ROGAINE should not be used by pregnant women.

Labor and Delivery: The effects are not known.

Nursing Mothers: ROGAINE should not be administered.

Pediatric Use. Safety and effectiveness has not been established under age 18.

ADVERSE REACTIONS

ROGAINE was used by 3,510 patients in placebo controlled trials. Except for dermatologic events, no individual reaction or reactions grouped by body systems appeared to be increased in the minoxidil-treated patients.

Respiratory (bronchitis, upper respiratory infection, sinusitis) 5.95%, **Dermatologic** (irritant or allergic contact dermatitis) 5.27%; **Gastrointestinal** (diarrhea, nausea, vomiting) 3.42%; **Neurologic** (headache, dizziness, faintness, light-headedness) 2.56%; **Musculoskeletal** (fractures, back pain, tendinitis) 2.17%; **Cardiovascular** (edema, chest pain, blood pressure increases/decreases, palpitation, pulse rate increases/decreases) 1.28%; **Allergic** (nonspecific allergic reactions, hives, allergic rhinitis, facial swelling, and sensitivity) 1.03%, **Special Senses** (conjunctivitis, ear infections, vertigo) 0.94%; **Metabolic-Nutritional** (edema, weight gain) 0.60%, **Urinary Tract** (urinary tract infections, renal calculi, urethritis) 0.46%; **Genital Tract** (prostatitis, epididymitis) 0.46%; **Psychiatric** (anxiety, depression, fatigue) 0.28%; **Hematologic** (lymphadenopathy, thrombocytopenia) 0.23%, **Endocrine** 0.09%.

Patients have been followed for up to 5 years, and there has been no change in incidence or severity of reported reactions. Additional events, not necessarily attributed to ROGAINE use, have been reported since marketing and include: eczema; hypertrichosis; local erythema, pruritus; dry skin/scalp flaking; sexual dysfunction; visual disturbances, including decreased visual acuity; exacerbation of hair loss; and alopecia.

DOSAGE AND ADMINISTRATION

Hair and scalp should be dry before application. 1 mL should be applied to the total affected areas twice daily. Total daily dose should not exceed 2 mL. If the fingertips are used to facilitate drug application, wash the hands afterwards.

HOW SUPPLIED

One 60-mL bottle with multiple applicators — NDC 0009-3367-05
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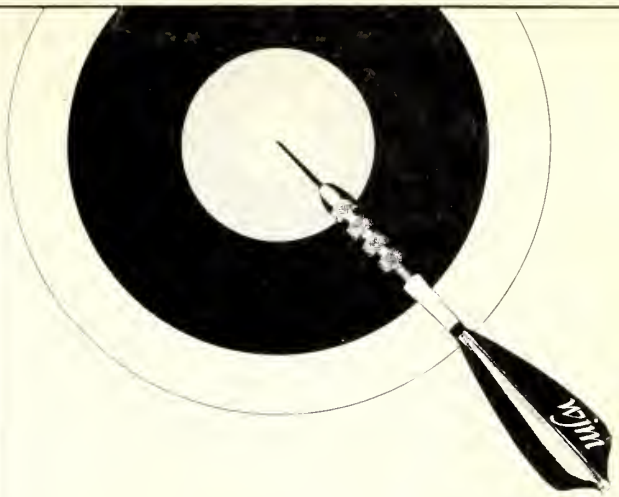

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Books

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5. Shusterman D: Espresso maker's wrist (Correspondence). West J Med 1990; 152:721-722

Government Publications

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7. Centers for Disease Control: Update: Acquired immunodeficiency syndrome—United States. MMWR 1987; 36:522-526

Proceedings

8. O'Connell M: A Controlled Trial of Regional Intra-arterial FUDR Versus Systemic 5FU for the Treatment of Metastatic Colorectal Cancer Confined to the Liver. Presented at the annual meeting of the American Society of Clinical Oncology, San Francisco, December 1989

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The Western Journal of Medicine

VOLUME 155 • NUMBER 1 • JULY 1991

CONTENTS

ARTICLES

27 **The Health Status of Minority Populations in the United States**

HERBERT W. NICKENS, MD, MA

From the Division of Minority Health, Disease Prevention/Health Promotion, Association of American Medical Colleges, Washington, DC.

33 **Fine Needle Aspiration Biopsy of Superficial Masses in Children**

LYDIA PLEOTIS HOWELL, MD; LISA A. RUSSELL, MD; P. HOLBROOK HOWARD, MD; and RAYMOND L. TEPLITZ, MD

From the Department of Pathology, University of California, Davis, Medical Center, Sacramento.

39 **Nonsteroidal Anti-inflammatory Drugs—Proposed Guidelines for Monitoring Toxicity**

THOMAS M. BUSH, MD; TAMMI L. SHLOTZHAUER, MD; and KENT IMAI, MD

From the Department of Medicine, Divisions of Rheumatology and Primary Care, Santa Clara Valley Medical Center, San Jose, California.

43 **Is Deleting the Digital Rectal Examination a Good Idea?**

MARK A. SUTTON; ROBERT P. GIBBONS, MD; and ROY J. CORREA, Jr, MD

From the University of Washington School of Medicine and the Section of Urology and Renal Transplantation, Virginia Mason Clinic, Seattle, Washington.

CONFERENCES AND REVIEWS

47 **The Clinical Diagnosis of Splenomegaly**

JACK C. YANG, MD, MPH; LELAND S. RICKMAN, MD; and SONYA K. BOSSER, MD

From the Department of Surgery, University of California, San Diego, Medical Center; the Division of Infectious Diseases, University of California, San Diego, Treatment Center; and the Department of Internal Medicine, National Naval Medical Center, Bethesda, Maryland.

53 **Understanding Osteoporosis**

ROBERT MARCUS, MD

From the Geriatric Research, Education and Clinical Center, Veterans Affairs Medical Center, Palo Alto, and the Department of Medicine, Division of Gerontology, Stanford University School of Medicine, Stanford, California.

61 **Painful Subacute Thyroiditis in Hawaii**

ROBERT A. NORDYKE, MD; FRED I. GILBERT, Jr, MD; and CHRIS LEW, MD

From the Department of Nuclear Medicine, Straub Clinic & Hospital, and the Department of Medicine, University of Hawaii John A. Burns School of Medicine, Honolulu, Hawaii.

EPITOMES—IMPORTANT ADVANCES IN CLINICAL MEDICINE

Neurology

Items of progress in neurology. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance.

64 **Use of Antiepileptic Drugs in Pregnancy**

MARIAN V. SOWA, MD

65 **Human T-cell Leukemia Virus Myelopathy**

WILLIAM A. SIBLEY, MD

(Continued on Page 12)

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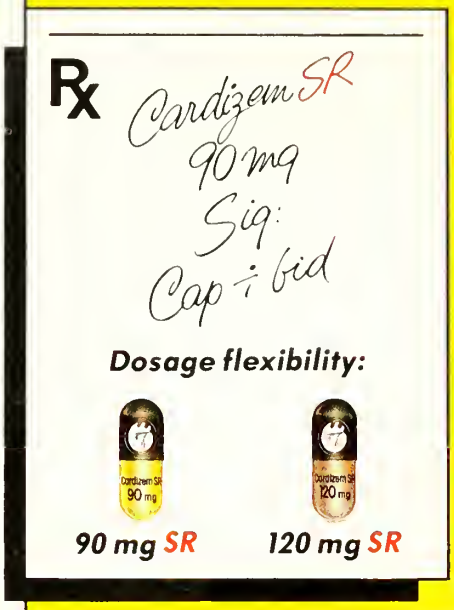

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WARNINGS

1. **Cardiac Conduction**. CARDIZEM prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second- or third-degree AV block (nine of 2,111 patients or 0.43%). Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single dose of 60 mg of diltiazem.
2. **Congestive Heart Failure**. Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). An acute study of oral diltiazem in patients with impaired ventricular function (ejection fraction 24% ± 6%) showed improvement in indices of ventricular function without significant decrease in contractile function (dp/dt). Experience with the use of CARDIZEM (diltiazem hydrochloride) in combination with beta-blockers in patients with impaired ventricular function is limited. Caution should be exercised when using this combination.
3. **Hypotension**. Decreases in blood pressure associated with CARDIZEM therapy may occasionally result in symptomatic hypotension.
4. **Acute Hepatic Injury**. Mild elevations of transaminases with and without concomitant elevation in alkaline phosphatase and bilirubin have been observed in clinical studies. Such elevations were usually transient and frequently resolved even with continued diltiazem treatment. In rare instances, significant elevations in enzymes such as alkaline phosphatase, LDH, SGOT, SGPT, and other phenomena consistent with acute hepatic injury have been noted. These reactions tended to occur early after therapy initiation (1 to 8 weeks) and have been reversible upon discontinuation of drug therapy. The relationship to CARDIZEM is uncertain in some cases, but probable in some. (See PRECAUTIONS.)

PRECAUTIONS

General. CARDIZEM (diltiazem hydrochloride) is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any drug given over prolonged periods, laboratory parameters should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes, however, these changes were reversible with continued dosing.

Dermatological events (see ADVERSE REACTIONS section) may be transient and may disappear despite continued use of CARDIZEM. However, skin eruptions progressing to erythema multiforme and/or exfoliative dermatitis have also been infrequently reported. Should a dermatologic reaction persist, the drug should be discontinued.

Drug Interaction. Due to the potential for additive effects, caution and careful titration are warranted in patients receiving CARDIZEM concomitantly with any agents known to affect cardiac contractility and/or conduction. (See WARNINGS.) Pharmacologic studies indicate that there may be additive effects in prolonging AV conduction when using beta-blockers or digitalis concomitantly with CARDIZEM. (See WARNINGS.)

As with all drugs, care should be exercised when treating patients with multiple medications. CARDIZEM undergoes biotransformation by cytochrome P-450 mixed function oxidase. Coadministration of CARDIZEM with other agents which follow the same route of biotransformation may result in the competitive inhibition of metabolism. Dosages of similarly metabolized drugs, particularly those of low therapeutic ratio or in patients with renal and/or hepatic impairment, may require adjustment when starting or stopping concomitantly administered CARDIZEM to maintain optimum therapeutic blood levels.

Beta-blockers: Controlled and uncontrolled domestic studies suggest that concomitant use of CARDIZEM and beta-blockers or digitalis is usually well tolerated, but available data are not sufficient to predict the effects of concomitant treatment in patients with left ventricular dysfunction or cardiac conduction abnormalities.

Administration of CARDIZEM (diltiazem hydrochloride) concomitantly with propranolol in five normal volunteers resulted in increased propranolol levels in all subjects and bioavailability of propranolol was increased approximately 50%. If combination therapy is initiated or withdrawn in conjunction with propranolol, an adjustment in the propranolol dose may be warranted. (See WARNINGS.)

Cimetidine: A study in six healthy volunteers has shown a significant increase in peak diltiazem plasma levels (58%) and area-under-the-curve (53%) after a 1-week course of cimetidine at 1,200 mg per day and diltiazem 60 mg per day. Ranitidine produced smaller, nonsignificant increases. The effect may be mediated by cimetidine's known inhibition of hepatic cytochrome P-450, the enzyme system probably responsible for the first-pass metabolism of diltiazem. Patients currently receiving diltiazem therapy should be carefully monitored for a change in pharmacological effect when initiating and discontinuing therapy with cimetidine. An adjustment in the diltiazem dose may be warranted.

Digitalis: Administration of CARDIZEM with digoxin in 24 healthy male subjects increased plasma digoxin concentrations approximately 20%. Another investigator found no increase in digoxin levels in 12 patients with coronary artery disease. Since there have been conflicting results regarding the effect of digoxin levels, it is recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing CARDIZEM therapy to avoid possible over- or under-digitalization. (See WARNINGS.)

Anesthetics: The depression of cardiac contractility, conductivity, and automaticity as well as the vascular dilation associated with anesthetics may be potentiated by calcium channel blockers. When used concomitantly, anesthetics and calcium blockers should be titrated carefully.

Carcinogenesis, Mutagenesis, Impairment of Fertility. A 24-month study in rats and a 21-month study in mice showed no evidence of carcinogenicity. There was also no mutagenic response in in vitro bacterial tests. No intrinsic effect on fertility was observed in rats.

Pregnancy. Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/postnatal studies, there was some reduction in early individual pup weights and survival rates. There was an increased incidence of stillbirths at doses of 20 times the human dose or greater.

There are no well-controlled studies in pregnant women, therefore, use CARDIZEM in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. Diltiazem is excreted in human milk. One report suggests that concentrations in breast milk may approximate serum levels. If use of CARDIZEM is deemed essential, an alternative method of infant feeding should be instituted.

Pediatric Use. Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Serious adverse reactions have been rare in studies carried out to date, but it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded from these studies.

The adverse events described below represent events observed in clinical studies of hypertensive patients receiving either CARDIZEM Tablets or CARDIZEM SR Capsules as well as experiences observed in studies of angina and during marketing. The most common events in hypertension studies are shown in a table with rates in placebo patients shown for comparison. Less common events are listed by body system; these include any adverse reactions seen in angina studies that were not observed in hypertension studies. In all hypertensive patients studied (over 900), the most common adverse events were edema (9%), headache (8%), dizziness (6%), asthenia (5%), sinus bradycardia (3%), flushing (3%), and 1° AV block (3%). Only edema and perhaps bradycardia and dizziness were dose related. The most common events observed in clinical studies (over 2,100 patients) of angina patients and hypertensive patients receiving CARDIZEM Tablets or CARDIZEM SR Capsules were (ie, greater than 1%) edema (5.4%), headache (4.5%), dizziness (3.4%), asthenia (2.8%), first-degree AV block (1.8%), flushing (1.7%), nausea (1.6%), bradycardia (1.5%), and rash (1.5%).

DOUBLE BLIND PLACEBO CONTROLLED HYPERTENSION TRIALS

Adverse	Diltiazem N=315 # pts (%)	Placebo N=211 # pts (%)
headache	38 (12%)	17 (8%)
AV block first degree	24 (7.6%)	4 (1.9%)
dizziness	22 (7%)	6 (2.8%)
edema	19 (6%)	2 (0.9%)
bradycardia	19 (6%)	3 (1.4%)
ECG abnormality	13 (4.1%)	3 (1.4%)
asthenia	10 (3.2%)	1 (0.5%)
constipation	5 (1.6%)	2 (0.9%)
dyspepsia	4 (1.3%)	1 (0.5%)
nausea	4 (1.3%)	2 (0.9%)
palpitations	4 (1.3%)	2 (0.9%)
polyuria	4 (1.3%)	2 (0.9%)
somnolence	4 (1.3%)	—
alk phos increase	3 (1%)	1 (0.5%)
hypotension	3 (1%)	1 (0.5%)
insomnia	3 (1%)	1 (0.5%)
rash	3 (1%)	1 (0.5%)
AV block second degree	2 (0.6%)	—

In addition, the following events were reported infrequently (less than 1%) or have been observed in angina trials. In many cases, the relation to drug is uncertain.

Cardiovascular: Angina, arrhythmia, bundle branch block, tachycardia, ventricular extrasystoles, congestive heart failure, syncope.
Nervous System: Amnesia, depression, gait abnormality, hallucinations, nervousness, paresthesia, personality change, tinnitus, tremor, abnormal dreams.
Gastrointestinal: Anorexia, diarrhea, dysgeusia, mild elevations of SGOT, SGPT, and LDH (see hepatic warnings), vomiting, weight increase, thirst.
Dermatological: Petechiae, pruritus, photosensitivity, urticaria.
Other: Amblyopia, CPK increase, dyspnea, epistaxis, eye irritation, hyperglycemia, sexual difficulties, nasal congestion, nocturia, osteoarticular pain, impotence, dry mouth.

The following postmarketing events have been reported infrequently in patients receiving CARDIZEM: alopecia, gingival hyperplasia, erythema multiforme, and leukopenia. Definitive cause and effect relationship between these events and CARDIZEM therapy cannot yet be established.

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ME-4966

(Continued from Page 6)

65 Acquired Immunodeficiency Syndrome Dementia
CHRISTINA MARRA, MD

66 Treatment of Cluster Headaches
DAVID C. AGNEW, MD

67 Electroencephalographic Brain Mapping
MARC R. NUWER, MD, PhD

67 Transcranial Doppler Study
KENNETH L. NUDLEMAN, MD

68 Myth of the Chronic Fatigue Syndrome
RONALD S. MURRAY, MD

68 Selegiline (Eldepryl) for Parkinson's Disease
CHERYL H. WATERS, MD, FRCPC

69 Intravenous γ-Globulin for Chronic Inflammatory Demyelinating Polyneuropathy and Myasthenia Gravis
JOHN C. KEESEY, MD

69 Botulinum Toxin Therapy
DANIEL D. TRUONG, MD

70 Preventing Chemotherapy-induced Neuropathy
KENNETH L. NUDLEMAN, MD

70 Carotid Endarterectomy
GREGORY K. CALL, MD

ALERTS, NOTICES, AND CASE REPORTS

72 Intravascular (Angiotropic) Large-cell Lymphoma ('Malignant Angioendotheliomatosis') With Small Vessel Pulmonary Vascular Obstruction and Hypercalcemia
JEFFREY L. CURTIS, MD; MARTHA L. WARNOCK, MD; DOUGLAS J. CONRAD, MD; LISA K. HELFEND, PhD, MD; and HOMER A. BOUSHEY, MD

From the Departments of Medicine and Pathology and the Cardiovascular Research Institute, University of California, San Francisco, School of Medicine, and the Respiratory Care Section, Medical Service, Veterans Affairs Medical Center, San Francisco, California. Dr Curtis is now with the Department of Veterans Affairs Medical Center, Ann Arbor, Michigan.

76 Resolution of Bowel Obstruction Due to Newly Diagnosed Inoperable Advanced Ovarian Cancer With Medical Therapy
THOMAS P. DRAKES, MD

From the Oncology Service, Redding Medical Center, Redding, California, and the Division of Hematology-Oncology, University of California, Davis, Medical Center, Sacramento.

78 Intractable Hiccups as a Presentation of Central Nervous System Sarcoidosis
LCDR JOHN P. CONNOLLY, MC, USN; LT TIMOTHY J. CRAIG, MC, USN; LCDR RAMÓN M. SANCHEZ, MC, USN; LCDR W. SCOTT SAGEMAN, MC, USN; and LCDR ROBIN E. OSBORN, MC, USN

From the Departments of Internal Medicine (Pulmonary Division), Neurology, Radiology, and Clinical Investigation, Naval Hospital, San Diego, California. Dr Connolly is currently with the Naval Hospital, Pensacola, Florida.

COMMENTARY

80 The Trial and Tribulation of Egerton Yorrick Davis
GERALD N. BURROW, MD

Dr Burrow is Professor of Medicine, Vice Chancellor for Health Sciences, and Dean, University of California, San Diego, School of Medicine, La Jolla.

(Continued on Page 16)

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ANESTHESIOLOGY

September 7-8—**Case Conference in Anesthesia.** California Society of Anesthesiologists at Horizon Hotel, Lake Tahoe, Nevada. Sat-Sun. 9 hrs. $150. Contact: California Society of Anesthesiologists, 1065 E Hillsdale Blvd, Ste 410, Foster City. (800) 345-3691.

September 14—**Current Concepts in Pediatric Anesthesia.** Children's Hospital, Oakland. Sun. 14 hrs. 7 hrs. $150. Contact: Children's Hospital, 747-52nd St, Oakland 94609. (415) 428-3021.

November 3-9—**Hawaiian Seminar on Clinical Anesthesia.** California Society of Anesthesiologists at Hyatt Regency Hotel, Poipu Beach, Kauai, Hawaii. 1 week. 20 hrs. $415. Contact: CSA, 1065 E Hillsdale Blvd, Ste 410, Foster City 94404. (800) 345-3691.

KEY TO ABBREVIATIONS

CMA California Medical Association
Contact: Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690. (415) 541-0900.

DREW Charles R. Drew Postgraduate Medical School
Contact: Herbert M. Thomas, MD, MPH, Director of CME, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th St, Los Angeles 90059. (213) 603-3183.

LLU Loma Linda University
Contact: James J. Couperus, MD, Associate Dean for Educational Affairs, Loma Linda University School of Medicine, Loma Linda 92350.

PMC Pacific Medical Center
Contact: Continuing Education, Pacific Medical Center, PO Box 7999, San Francisco 94120. (415) 563-4321, ext 2761.

STAN Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Medical School Office Building, Suite X-365, Stanford 94305-6114. (415) 723-5594.

UCD University of California, Davis
Contact: Ruth Feryok, Director, Office of Continuing Medical Education, University of California, Davis, School of Medicine, 2701 Stockton Blvd, Sacramento 95817. (916) 734-5390.

UCI University of California, Irvine
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UCLA University of California, Los Angeles Extension
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UCSD University of California, San Diego
Contact: Office of Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (619) 534-3940.

UCSF University of California, San Francisco
Contact: Janet Johnson, Administrative Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 476-4251.

USC University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 1975 Zonal Ave, KAM314, Los Angeles 90033. (213) 224-7051.

November 8-10—**Anesthesiology Update: 1991.** UCD at Monterey Plaza Hotel, Monterey. Fri-Sun. 14 hrs. $370. Contact: UCD.

CARDIOLOGY

August 1-3—**Critical Care Cardiology.** UCSF at Sheraton Palace Hotel, San Francisco. Thurs-Sat. 15 hrs. Contact: UCSF.

August 2-4—**Arrhythmias: Interpretation, Diagnosis and Management.** Medical Education Resources at Sheraton Hotel, Monterey. Fri-Sun. Contact: Medical Education Resources, 1500 W Canal Ct, Ste 500, Littleton, CO 80120. (800) 421-3756.

August 16-18—**Cardiac Diagnostic Methods and Risk Management.** Medical Education Resources at Disneyland Hotel, Anaheim. Fri-Sun. Contact: Medical Education Resources, 1500 W Canal Ct, Ste 500, Littleton, CO 80120. (800) 421-3756.

October 10-12—**Cardiology Update: 1991.** American College of Cardiology at Quail Lodge, Carmel. Thurs-Sat. 12.5 hrs. $440. Contact: ACC, Extramural Programs, Dept 5080, Washington, DC 20061-5080. (800) 253-4636.

October 18-19—**Coronary Heart Disease Update.** Medical Education Resources at Parc Fifty Hotel, San Francisco. Fri-Sat. Contact: Karen DeBont, MER, 1500 W Canal Ct, Ste 500, Littleton, CO 80120-4528. (800) 421-3756.

October 18-19—**Cardiology for the Clinician.** Memorial/UCI Center for Health Education. Fri-Sat. Contact: UCI.

November 8-9—**Coronary Interventions: 1991.** Scripps Clinic and Research Foundation at La Jolla Marriott Hotel. Fri-Sat. 14 hrs. $550. Contact: Susan Buntjer, 400S, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

CRITICAL CARE

October 17-19—**Traumatic Brain Injury.** UCD at Radisson Hotel, Sacramento. Thurs-Sat. 26 hrs. Contact: UCD.

October 17-19—**10th Annual Recent Advances in Pulmonary and Critical Care Medicine.** UCSF at Sheraton Palace Hotel, San Francisco. Thurs-Sat. 15 hrs. $395. Contact: UCSF.

DERMATOLOGY

July 16-20—**Dr. Hugh Greenway's Seventh Annual Conference: Superficial Anatomy and Cutaneous Surgery.** Scripps Clinic and Research Foundation/UCSD at Scripps Clinic, La Jolla. Tues-Sat. 36 hrs. $1100. Contact: Susan J. Buntjer, 10666 N Torrey Pines Road, La Jolla 92037. (619) 554-8556.

July 19-21—**Contact Dermatitis: The Basics.** Stanford at Hotel Meridien, San Francisco. Fri-Sun. Contact: Pamela Bain, Dept of Dermatology, Room R-122, Stanford 94305. (415) 723-7854.

August 16-20—**Fifth Annual Hot Spots in Dermatology: Masters Under the Mango Trees.** The Hawaii Dermatology Society and the Kauai Foundation at the Kaluakoi Hotel, Kepuhi Beach, Molokai, Hawaii. Fri-Tues. Contact: David Elpern, MD, Box 457, Kalaheo, HI 96741. (808) 245-1505.

August 26-28—**Dermatology for the Nondermatologist.** Continuing Medical Education Associates at Hotel del Coronado, San Diego. Mon-Wed. Contact: Jacqueline Shiller, Box 84296, San Diego 92138. (619) 223-2997.

November 8-10—**Pediatric Dermatology and Wound Management: Above and Below the Surface.** Children's Hospital Oakland at Monterey Conference Center, Monterey. Fri-Sun. 12 hrs. $300. Contact: Children's Hospital, 747-52nd St, Oakland 94609. (415) 428-3021.

EMERGENCY MEDICINE

July 18-21—**Topics in Emergency Medicine.** American College of Physicians at Hyatt Regency Embarcadero, San Francisco. Thurs-Sun. $389. Contact: ACP, Independence Mall West, 6th St at Race, Philadelphia, PA 19106-1572. (800) 523-1546, ext. 2429.

August 1-3—**Debates and Updates in Pediatric Emergency Medicine.** UCSF at San Francisco Hilton Hotel, San Francisco. Thurs-Sat. 18 hrs. $350. Contact: UCSF.

(Continued on Page 18)

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(Continued from Page 12)

EDITORIALS

83 **Subacute Thyroiditis**
MONTE A. GREER, MD
Dr Greer is Professor of Medicine, Section of Endocrinology, Oregon Health Sciences University, Portland.

83 **Two Medical Worlds—Separate and Unequal**
WOODROW A. MYERS, Jr, MD, MBA
Dr Myers is the City Health Commissioner, New York City Department of Health, New York.

CORRESPONDENCE

86 **Redwood Medicare Assignment Program**
HERBERT NOTKIN, MD

86 **Cancer Patients and Support Groups**
HAROLD H. BENJAMIN, PhD, and MICHAEL S. GOLDSTEIN, PhD

LESSONS FROM THE PRACTICE

87 **The Sailor Who Couldn't Play Pool**
PAUL L. KINGSLEY, MD
Dr Kingsley is currently retired from private practice in psychiatry and neurology and lives in Ross, California.

88 **Concerned Patient**
EDMUND VAN BRUNT, MD
Dr Van Brunt recently retired as Director of the Division of Research, Kaiser Permanente Medical Care Program, Oakland, California.

OTHER FEATURES

2 **Instructions for Authors**

14 **Continuing Medical Education Activities in California, Hawaii, and Nevada; Colorado; Idaho; New Mexico; Utah; Washington; Wyoming**

25 **Subscription Information**

94 **Classified Advertising**

106 **Western State Medical Associations' Meetings**

Poems: 38, 46, 82

★ Official Journal of the Alaska State Medical Association, the Arizona Medical Association, the California Medical Association, the Denver Medical Society, the Idaho Medical Association, the Nevada State Medical Association, the New Mexico Medical Society, the Utah Medical Association, the Washington State Medical Association, and the Wyoming Medical Society.

★ Affiliated Clinical Investigation Societies: the Western Association of Physicians; the Western Society for Clinical Investigation; the Western Section, American Federation for Clinical Research; the Western Society for Pediatric Research; the Western Region, Society for Investigative Dermatology.

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CONTINUING MEDICAL EDUCATION

(Continued from Page 14)

August 7-11—**Wilderness Medicine: '91.** American College of Emergency Physicians at Squaw Valley, Lake Tahoe. Wed-Sun. 22 hrs. Contact: Program Director, Box 321, Yreka 96097. (800) 888-5632.

August 19-23—**Symposium II: Trauma and Surgery.** UCSD at La Jolla Marriott, La Jolla. Mon-Fri. 32 hrs. $485. Contact: UCSD.

August 23-26—**Advances in Emergency Medicine.** Kaiser Permanente at Grand Hyatt Wailea Resort and Spa, Maui, Hawaii. Fri-Mon. Contact: Pat Salber, MD, Kaiser Permanente Hospital, 2200 O'Farrell, San Francisco 94115-3395.

October 28-November 1—**Twentieth Annual Topics in Emergency Medicine.** UCSF at Sheraton Palace Hotel, San Francisco. Mon-Fri. 32 hrs. $510. Contact: UCSF.

ENDOCRINOLOGY AND METABOLISM

October 18-20—**Obesity Update: Assessment & Treatment.** UCD at Hyatt Regency, Sacramento. Fri-Sun. Contact: UCD.

October 20-23—**Joint Annual Research Conference on Obesity & Food Intake.** North American Association of the Study of Obesity & Society for Study of Ingestive Behavior at Hyatt Regency, Saramento. Sun-Wed. Contact: UCD.

November 1-2—**Practical Methods in Diabetes.** Memorial/UCI Center for Health Education at Meridien Newport Beach. Fri-Sat. Contact: UCD.

FAMILY PRACTICE/PRIMARY CARE

August 23-25—**Cardiology for the Family Physician and Internist.** Continuing Medical Education Associates at Hotel del Coronado, San Diego. Fri-Sun. Contact: Jacqueline Shiller, Box 84296, San Diego 92138. (619) 223-2997.

August 23-25—**4th Coronado Summer Conference on Primary Care Medicine: A Practical Approach.** Scripps Clinic and Research Foundation at Le Meridien Hotel, San Diego. Fri-Sun. 16 hrs. $275. Contact: Laurie Jones, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-9592.

October 2-4—**Sixth Annual Primary Care Medicine: Principles and Practice.** UCSF at Sheraton Palace Hotel, San Francisco. Wed-Fri. 19 hrs. $465. Contact: UCSF.

October 18-20—**Office Orthopedics for the Primary Care Physician.** Sharp Memorial Hospital at San Diego Princess at Vacation Village. Fri-Sun. 20 hrs. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

GASTROENTEROLOGY

July 15-19—**Advances in Gastroenterology.** UCSD at Hotel del Coronado, San Diego. Mon-Fri. 19-22 hrs. $425. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

September 20-22—**Gastroenterology: Recent Developments in Theory & Practice.** UCSF at Sheraton Palace Hotel, San Francisco. Fri-Sun. 18 hrs. $420. Contact: UCSF.

INTERNAL MEDICINE

August 1-3—**4th Annual New Advances in Common Neurologic Disorders.** UCSD at Catamaran Resort Hotel, San Diego. Thurs-Sat. $300. Contact: Shirley Kolkey, 5665 Oberlin Dr, Ste 110, San Diego 92121. (619) 453-6222.

August 5-9—**Internal Medicine: 39th Annual Update and Board Review Course.** American College of Physicians and USC at Health Sciences Center, Los Angeles. Mon-Fri. Contact: ACP, Independence Mall West, 6th St at Race, Philadelphia, PA 19106-1572. (800) 523-1546, ext. 2429.

August 18-23—**New Advances in Internal Medicine.** UCD at Hyatt Regency, Monterey. Sun-Fri. 25 hrs. $460. Contact: UCD.

August 26-30—**Internal Medicine Board Review.** Stanford University Medical Center. Mon-Fri. Contact: STAN.

September 6-7—**Cancer Detection & Management.** UCD at Cancer Center Auditorium. Fri-Sat. 12 hrs. Contact: UCD.

September 28—**Pain: Diagnosis, Treatment and Management.** Scripps Clinic and Research Foundation, La Jolla. Sat. 19 hrs. $75. Contact: Laurel Steigerwald, 10666 N Torrey Pines Road, La Jolla 92037. (619) 554-8556.

October 14-20—**Seventeenth Annual Lymphoma Course.** Scripps Clinic and Research Foundation, La Jolla. Mon-Fri. 25 hrs. $550. Contact: Laurel Steigerwald, 10666 N Torrey Pines Road, La Jolla 92037. (619) 554-8556.

November 2—**Lipids Update.** UCD at Radisson Hotel, Sacramento. Sat. Contact: UCD.

November 7-9—**San Francisco Otology Update: 1991.** UCSF. Thurs-Sat. 22 hrs. Contact: UCSF.

November 15-16—**Pain Management.** UCD at Sterling Hotel, Napa. Fri-Sat. Contact: UCD.

November 21-23—**3rd Annual Symposium on Diagnosis and Treatment of Bone and Soft Tissue Tumors.** UCD at Hyatt Regency, Sacramento. Thurs-Sat. Contact: UCD.

December 5—**Common Musculoskeletal Problems—Knee.** VA Medical Center Sepulveda. Thurs. 5.5 hrs. Contact: Arun Mehta, MD, VA Med Ctr, (818) 895-9344.

December 6-7—**Clinical Applications of New Advances in Internal Medicine.** UCD at Cancer Center Auditorium. Fri-Sat. Contact: UCD.

OB/GYN

July 28-31—**4th Annual In Vitro Fertilization and Embryo Transfer: A Comprehensive Update—1991.** Sun-Wed. 15 hrs. $675. Contact: UCLA Extension.

July 31—**9th Controversies in OB/GYN.** Memorial/UCI Center for Health Education in Hawaii. Wed-Sat. Contact: UCI.

August 9-11—**4th Annual Perinatal Review.** Memorial/UCI Center for Health Education at Four Seasons Hotel, Newport Beach. Fri-Sun. Contact: Memorial/UCI Center for Health Education, Box 1428, Long Beach 90801. (213) 595-3811.

August 16-18—**Office Gynecology for the Primary Care Physician.** San Diego State University at the Hyatt Islandia, San Diego. Fri-Sun. Contact: Jacqueline Shiller, Box 84296, San Diego 92138. (619) 223-2997.

September 26-29—**Advanced Fetal Heart Rate Monitoring.** Memorial/UCI Center for Health Education. Thurs-Sun. Contact: UCI.

October 4-6—**3rd Annual Advanced Obstetrical & Transvaginal Ultrasound.** Memorial/UCI Center for Health Education at Doubletree Hotel/UCI Medical Center, Orange. Fri-Sun. Contact: UCI.

November 8-10—**Current Issues in Perinatal Medicine.** Memorial/UCI at Marriott's Rancho Las Palmas Resort, Palm Springs. Fri-Sun. Contact: UCI.

November 18-23—**14th Annual Review Course in Clinical Ob/Gyn and Gynecological Histopathology.** Memorial/UCI Center for Health Education at Westin South Coast Plaza, Costa Mesa. Mon-Sat. Contact: UCI.

OCCUPATIONAL/ENVIRONMENTAL

June 22—**Workers' Compensation Seminar.** American College of Occupational Medicine in San Francisco. Sat. 6 hrs. $150. Contact: California Workers' Compensation Institute. (415) 981-2107.

October 10-13—**35th Annual Western Occupational Health Conference: Changing Themes in Occupational Medicine.** Western Occupational Medical Association at Doubletree Hotel, Monterey. Thurs-Sun. Contact: Kate Larsen, (415) 764-4803.

October 21-25—**Sports Medicine Update.** Memorial/UCI Center for Health Education in Hawaii. Mon-Fri. Contact: UCI.

October 21-November 1—**Occupational and Environmental Medicine: Session II.** UCSF at Miyako Hotel, San Francisco. Mon-Fri. 80 hrs. $1200. Contact: UCSF.

October 28-November 1—**Advances in Occupational and Environmental Medicine.** UCSF at Miyako Hotel, San Francisco. Mon-Fri. 40 hrs. $600. Contact: UCSF.

OPHTHALMOLOGY

September 13-15—**Uveitis and Retina Frontiers—Diagnostic, Medical and Surgical Approaches.** UCSF at Carmel Valley Ranch Resort. Fri-Sun. Contact: UCSF.

October 13-17—**Joint Meeting of the American Academy of Ophthalmology and Pan-American Association of Ophthalmology** at Anaheim Convention Center. Sun-Thurs. Contact: AAO, PO Box 7424, San Francisco 94120. (415) 561-8500.

PATHOLOGY

August 9-10—**Southwestern Regional Cryostat and Microscopically Controlled Surgical Workshop.** UCSD. Fri-Sat. 15 hrs. Contact: Daniel E. Gormley, MD, 412 W Carroll Dr, Ste 207, Glendora 91740. (818) 963-7684.

(Continued on Page 22)

What we've done for you lately.

We've taken some concrete steps toward making the less exciting parts of your job less of a problem.

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Their Blood...

- In the average smoker (20 to 30 cigarettes a day), physiologic nicotine addiction is reinforced with every cigarette

Peak blood levels produce physiologic satisfaction and reinforcement. Craving occurs when the concentration sinks to a lower level, which the smoker will satisfy with the next cigarette.

On cessation of smoking and initiation of therapy with Nicorette, the patient's nicotine blood levels may be reduced by approximately 50% or more, eliminating the sharp peaks which perpetuate dependence.

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- 43% of smokers age 35 and over have tried to quit three times or more
- 80% of efforts are unsuccessful
- Fear of the medical risks of smoking is real, intense, and well-documented

Add Control to Commitment

Enhancing the Comfort Level Adds Control to Commitment

Relief of craving can make a world of difference. When used in conjunction with a program of behavior modification under medical supervision, Nicorette can help provide the committed quitter with:

- Relief of physical craving
- Immediate freedom from worry about carcinogens and carbon monoxide
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Used properly...

Nicorette®

(nicotine polacrilex)

Relieves Craving...
Reinforces Commitment

Please see the brief summary of prescribing information on the adjacent page.

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BRIEF SUMMARY

Nicorette® (nicotine polacrilex)

CAUTION Federal law prohibits dispensing without prescription

DESCRIPTION. Each piece of Nicorette contains nicotine polacrilex equivalent to 2 mg nicotine and also contains flavors, glycerin gum base sodium bicarbonate, sodium carbonate, and sorbitol

INDICATION AND USAGE: Nicorette is indicated as a temporary aid to the cigarette smoker seeking to give up his or her smoking habit while participating in a behavioral modification program under medical or dental supervision For further information, please see Full Prescribing Information

CONTRAINDICATIONS Nicorette is contraindicated in non smokers

Nicorette is contraindicated in patients during the immediate post myocardial infarction period, patients with life-threatening arrhythmias, and patients with severe or worsening angina pectoris (See WARNINGS)

Also, Nicorette is contraindicated in patients with active temporomandibular joint disease

Current medical opinion indicates that nicotine in any form may be harmful to an unborn child Nicorette and cigarettes both contain nicotine

Nicorette may cause fetal harm when administered to a pregnant woman

Use of cigarettes or Nicorette during the last trimester has been associated with a decrease in fetal breathing movements These effects may be the result of decreased placental perfusion caused by nicotine Rare reports of miscarriages have been received, and a relationship to drug therapy as a contributing factor cannot be excluded Studies in pregnant rhesus monkeys have shown that maternal nicotine administration produced acidosis, hypoxia and hypercarbia in the fetus

Nicotine has been shown to be teratogenic in mice treated subcutaneously with 25 mg/kg which is approximately 300 times the human buccal dose Studies in rats and monkeys have not demonstrated a teratogenic effect of nicotine in doses which would occur during cigarette smoking

Nicorette is therefore contraindicated in women who are or may become pregnant, and female patients should be advised to take adequate precautions to avoid becoming pregnant The physician may wish to consider a pregnancy test before instituting therapy with Nicorette If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus

WARNINGS The risks of nicotine in patients with certain cardiovascular and endocrine diseases should be carefully weighed against the benefits of including Nicorette in a smoking cessation program in these patients Specifically patients with coronary heart disease (history of myocardial infarction and/or angina pectoris), serious cardiac arrhythmias, or vasospastic diseases (Buerger's disease Prinzmetal variant angina) should be carefully screened and evaluated before Nicorette is prescribed Occasional reports of tachyarrhythmias occurring in association with the use of Nicorette have been reported, therefore, if an increase in cardiovascular symptoms occurs with the use of Nicorette, it should be discontinued

As the action of nicotine on the adrenal medulla (release of catecholamines) does not appear to be affected by tolerance Nicorette should be used with caution in patients with hyperthyroidism, pheochromocytoma or insulin-dependent diabetes Cigarette smoking is felt to play a perpetuating role in hypertension and peptic ulcer disease Therefore, Nicorette should be used in patients with systemic hypertension or peptic ulcer (active or inactive) only when the benefits of including Nicorette in a smoking cessation program outweigh the risks

PRECAUTIONS Nicorette should be used with caution in patients with oral or pharyngeal inflammation and in patients with a history of esophagitis or peptic ulcer

The dosage form of Nicorette dictates that it be used with caution in patients whose dental problems might be exacerbated by chewing gum In such patients prior dental evaluation may be advisable

Nicorette is sugar-free and has been formulated to minimize stickiness As with other gums, however, the degree to which Nicorette may stick to dentures, dental caps or partial bridges may depend on the materials from which they are made and other factors such as amount of saliva produced, possible interaction with denture adhesives, denture cleaning compounds, dryness of mouth due to other causes and salivary constituents Should an excessive degree of stickiness to dental work occur there is a possibility that as with other gums, Nicorette may damage dental work, if this should occur, the patient should discontinue its use and consult a physician or dentist

The sustained use of Nicorette by ex-smokers is not to be encouraged because the chronic consumption of nicotine is toxic and addicting The physician must however weigh the relative risks of a possible return to smoking versus continued, long-term use of the gum

Information for Patients The patient instruction sheet is attached at the end of the professional labeling text It is intended for detachment by the pharmacist and inclusion in the package of Nicorette dispensed to the patient It contains important selected information on patient selection risks and adverse effects and instructions on how to use Nicorette properly

Drug Interactions Smoking cessation with or without nicotine substitutes, may alter response to concomitant medication in ex-smokers Smoking is considered to increase metabolism and thus lower blood levels of drugs such as phenacetin, caffeine theophylline imipramine and pentazocine through enzyme induction Cessation of smoking may result in increased levels of these drugs Absorption of glutethimide may be decreased and the first pass metabolism of propoxyphene may be decreased by smoking cessation Other reported effects of smoking, which do not involve enzyme induction, include reduced diuretic effects of furosemide and decreased cardiac output and increased blood pressure with propranolol which may also relate to the hormonal effects of nicotine Smoking cessation may reverse these actions

Both smoking and nicotine can increase circulating cortisol and catecholamines Therapy with adrenergic agonists or with adrenergic blockers may need to be adjusted according to changes in nicotine therapy or smoking status

Carcinogenesis Mutagenesis Impairment of Fertility Nicotine was not mutagenic in the Ames *Salmonella* test

Literature reports indicate that nicotine is neither an initiator nor a tumor-promoter in mice There is inconclusive evidence to suggest that cotinine an oxidized metabolite of nicotine may be carcinogenic in rats Cotinine was not mutagenic in the Ames *Salmonella* test

Studies have shown a decrease of litter size in rats treated with nicotine during the time of fertilization

Pregnancy Pregnancy Category X (See CONTRAINDICATIONS)

Nursing Mothers Nicotine passes freely into the breast milk Because of the potential for serious adverse reactions in nursing infants from nicotine a decision should be made whether to discontinue nursing or to discontinue the drug taking into account the importance of the drug to the mother

Pediatric Use Safety and effectiveness in children and adolescents who smoke have not been evaluated

ADVERSE REACTIONS Adverse reactions reported in association with the use of Nicorette include both local effects and systemic effects representing the pharmacologic action of nicotine Rare reports of an apparent severe allergic reaction have been received

Local side effects Mechanical effects of gum chewing include traumatic injury to oral mucosa or teeth jaw ache and eructation secondary to air swallowing These side effects may be minimized by modifying chewing technique Oral mucosal changes such as stomatitis glossitis gingivitis pharyngitis and aphthous ulcers in addition to changes in taste perception, can occur during smoking cessation efforts with or without the use of Nicorette

Systemic side effects Although the systemic effects seen in trials were generally similar the reported frequency of adverse drug effects was highly variable as illustrated by the variation observed in adverse event incidences estimated from the results of two well controlled studies (one performed in the United States and the other in England) designed to evaluate the safety and efficacy of Nicorette (See table below) Given this variability the table can be used only as an indication of the relative frequency of adverse events reported in representative clinical trials It can not predict expected incidences of these effects during the course of usual medical practice

Treatment Emergent
Symptom Incidence for the 2 mg Gum

	US		British	
	Drug	Placebo	Drug	Placebo
Number of Subjects Reporting	94	95	58	58
Percent of Subjects Reporting				
Autonomic				
Excess Salivation	2 1	0 0		
CNS				
Insomnia	1 1	1 1		
Dizziness/Light-headedness	2 1	2 1	19 0	13 8
Irritable/Fussy	1 1	1 1		
Headache	1 1	5 3	24 1	29 3
Gastrointestinal				
Nonspecific GI Distress	9 6	6 3		
Eructation	6 4	1 1		
Indigestion			41 4	20 7
Nausea/Vomiting	18 1	4 2	31 0	15 5
Reactions Referable to Mouth Throat Jaw or Teeth				
Mouth or Throat Soreness	37 2	31 6	56 9	53 4
Jaw Muscle Ache	18 1	9 5	44 8	44 8
Others				
Anorexia	1 1	1 1		
Hiccups	14 9	0 0	22 4	3 4

The only potentially serious systemic adverse effect observed among the 152 patients evaluated in the controlled clinical trials used to support the efficacy of Nicorette was cardiac irritability a patient displayed what may have been nicotine-induced but reversible atrial fibrillation Cardiac irritability is a well known consequence of cigarette smoking

A 46-year-old male patient participating in a clinical trial of Nicorette was reported to have developed nicotine intoxication requiring his hospitalization After 4 days he was discharged fully recovered He died suddenly one month later Nicorette was not used during this one-month interval The relationship of the patient's death to his prior treatment is undetermined

Since the marketing of Nicorette in the US reports of several other deaths and reports including myocardial infarction congestive heart failure cerebrovascular accident and cardiac arrest have been received A cause and effect relationship between these reports and the use of Nicorette has not been established

In addition to the reported effects listed above the following events have been reported *CARDIOVASCULAR*—edema flushing hypertension palpitations tachyarrhythmias tachycardia *CNS*—confusion convulsions depression euphoria numbness paresthesia syncope tinnitus weakness *DERMATOLOGIC*—erythema itching rash urticaria *GASTROINTESTINAL*—alteration of liver function tests constipation diarrhea *RESPIRATORY*—breathing difficulty cough hoarseness sneezing wheezing *OTHER*—dry mouth systemic nicotine intoxication

Rare reports of miscarriages have been received and a relationship to drug therapy as a contributing factor cannot be excluded

DRUG ABUSE AND DEPENDENCE/OVERDOSE/TREATMENT OF OVERDOSAGE For further information please see full prescribing information

DOSAGE AND ADMINISTRATION Most patients require approximately 10 to 12 pieces of gum per day during the first month of treatment Patients should be instructed not to exceed 30 Nicorette pieces per day Patients should be assessed after one month of treatment to determine smoking status and the use of Nicorette as an adjunct should be reevaluated Gradual withdrawal from Nicorette should be initiated after 3 months usage and completed by 6 months The use of Nicorette beyond 6 months is not recommended

Product Information as of May 1989

Manufactured by Akhebolaget Leo Helsingborg Sweden for
MARION MERRELL DOW INC
Prescription Products Division
Kansas City MO 64114

NICAE 703/0202 6320HH

CONTINUING MEDICAL EDUCATION

(Continued from Page 18)

October 12—**Thirty-first Annual Scientific Symposium on Kidney Disease.** National Kidney Foundation of Southern California at La Jolla Marriott, La Jolla. Sat. Contact: Sylvie Tarro, (213) 641-8152.

PEDIATRICS

August 19-21—**Pediatrics Update: 1991.** San Diego State University at the Hyatt Islandia, San Diego. Mon-Wed. Contact: Jacqueline Shiller, Box 84296, San Diego 92138. (619) 223-2997.

September 13-14—**Ambulatory Pediatrics.** UCD at Radisson Hotel, Sacramento. Fri-Sat. 12 hrs. Contact: UCD.

October 16-19—**16th Annual Pediatrics for the Practitioner.** Memorial/UCI Center for Health Education at Mauna Kea Beach Hotel, Kamuela, Hawaii. Wed-Sat. Contact: UCI.

November 20-23—**Pediatric Infectious Disease Seminar.** University of Toronto at Four Seasons Hotel, Newport Beach. Wed-Sat. Contact: University of Toronto, Medical Science Bldg, Toronto, Ontario M5S 1A8. (416) 978-2718.

PSYCHIATRY

July 27-28—**Treatment of Sexual Problems of Adults Molested as Children.** UCLA at Beverly Hilton Hotel. Sat-Sun. 13 hrs. $275. Contact: UCLA.

November 8-10—**37th Annual Group Therapy Symposium.** UCSF at Handlery Union Square Hotel, San Francisco. Fri-Sun. Contact: UCSF.

RADIOLOGY

July 18-21—**Radiology for Non-Radiologists.** UCSD at Hotel del Coronado, Coronado. Thurs-Sun. 19.5 hrs. $400. Contact: Dawne Ryals, Box 1925, Roswell, GA 30077. (404) 641-9773.

July 22-24—**Issues in Musculoskeletal Imaging.** Hoag Memorial Hospital at Ritz-Carlton Hotel, Laguna Niguel. Mon-Wed. 14 hrs. $375. Contact: Dawne Ryals, Box 1925, Roswell, GA 30077. (404) 641-9773.

July 22-27—**5th Annual MRI Symposium Including: Issues in Musculoskeletal Imaging.** Hoag Memorial Hospital at Ritz-Carlton Hotel, Laguna Niguel. Mon-Sat. 31 hrs. $695. Contact: Dawne Ryals, Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

July 25-28—**5th Annual Symposium on Magnetic Resonance Imaging.** Hoag Memorial Hospital at Ritz-Carlton Hotel, Laguna Niguel. Thurs-Sun. 18 hrs. $375. Contact: Dawne Ryals, Box 1925, Roswell, GA 30077. (404) 641-9773.

July 29-August 2—**MRI: Musculoskeletal/Body.** UCSF at Hyatt Regency, Kauai, Hawaii. Mon-Fri. 22 hrs. $595. Contact: UCSF.

August 4-8—**Napa Valley Imaging Update-MRI 1991.** UCD at Silverado Country Club, Napa. Sun-Thurs. 17 hrs. $465. Contact: UCD.

August 12-16—**Radiology for Clinicians.** UCSD at Hotel del Coronado, San Diego. Mon-Fri. Contact: Dawne Ryals, Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

September 5-8—**Physics of Diagnostic Radiology, Nuclear Medicine and Radiation Biology.** UCD. Thurs-Sun. 25 hrs. $395. Contact: UCD.

September 11-13—**The 7th Annual Sonography Update Conference and Exhibit.** UCSD at Hotel del Coronado, San Diego. Wed-Fri. 18 hrs. $400. Contact: Dawne Ryals, Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

September 14-15—**Sonography Registry Review.** UCSD at Hotel del Coronado, San Diego. Sat-Sun. 16 hrs. $200. Contact: Dawne Ryals, Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

September 23-26—**Applied Ultrasound: Accent on Doppler.** University of Alabama at Birmingham at Ritz-Carlton Resort Hotel, Laguna Niguel. Mon-Thurs. Contact: Dawne Ryals, Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

September 25-28—**Diagnosis of Musculoskeletal Disorders: State of the Art.** International Skeletal Society at Hotel del Coronado, San Diego. Wed-Sat. 28 hrs. $450. Contact: Dawne Ryals, Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

October 2-6—**Current Concepts of Magnetic Resonance Imaging/Physics.** Stanford University Medical Center at Silverado Hotel, Napa Valley. Wed-Mon. 19 hrs. $500. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

October 12-13—**Ultrasound: 1991.** UCD at Red Lion Inn, Sacramento. Sat-Sun. 10 hrs. $215. Contact: UCD.

October 17-20—**1991 Annual Scientific Meeting.** Western Neuroradiological Society at Ritz Carlton Resort, Laguna Niguel. Thurs-Sun. Contact: Dawne Ryals, Ryals & Associates, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

(Continued on Page 24)

If you want to know what ROGAINE® can do, ask the people who use it.

"I like to look good: that's why I wanted to try ROGAINE in the first place. There's no doubt it's working for me...and because my hair is growing, so is my confidence."—TONY VILA, JR

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Rogaine® Rx
TOPICAL SOLUTION
minoxidil 2%

ANY DIFFERENCE MEANS A LOT.

Please see adjacent page for brief summary of prescribing information.

*Data on file, The Upjohn Company.

Upjohn | DERMATOLOGY DIVISION

Rogaine® Rx

TOPICAL SOLUTION minoxidil 2%

INDICATIONS AND USAGE

ROGAINE is indicated for treatment of male pattern baldness (alopecia androgenetica) of the vertex of the scalp. At least 4 months of treatment is generally required before evidence of hair growth can be expected, further growth continues through 1 year of treatment

CONTRAINDICATIONS

Hypersensitivity to minoxidil, propylene glycol, or ethanol.

WARNINGS

1 Need for normal scalp. Before starting treatment, make sure that the patient has a normal, healthy scalp. Local abrasion or dermatitis may increase absorption and hence the risk of side effects.

2. Potential adverse effects Although extensive use of topical minoxidil has not revealed evidence that enough minoxidil is absorbed to have systemic effects, greater absorption because of misuse, individual variability, or unusual sensitivity could, at least theoretically, produce a systemic effect.

Experience with oral minoxidil has shown the following major cardiovascular effects (Review the package insert for LONITEN® Tablets for details):

– salt and water retention, generalized and local edema
– pericardial effusion, pericarditis, tamponade
– tachycardia
– increased incidence of angina or new onset of angina

Patients with underlying heart disease, including coronary artery disease and congestive heart failure, would be at particular risk of these potential effects Additive effects could also emerge in patients being treated for hypertension.

Potential patients should have a history and physical and should be advised of potential risks A risk/benefit decision should be made Heart patients should realize that adverse effects may be especially serious.

Alert patients to the possibility of tachycardia and fluid retention and monitor for increased heart rate, weight gain, or other systemic effects.

PRECAUTIONS

General Precautions: Monitor patients 1 month after starting ROGAINE and at least every 6 months afterward Discontinue ROGAINE if systemic effects occur.

The alcohol base will burn and irritate the eye. If ROGAINE reaches sensitive surfaces (eg, eye, abraded skin, and mucous membranes), bathe with copious cool water.

Avoid inhaling the spray

Do not use in conjunction with other topical agents such as corticosteroids, retinoids and petrolatum, or agents that enhance percutaneous absorption.

ROGAINE is for topical use only Each mL contains 20 mg minoxidil and accidental ingestion could cause adverse systemic effects

Decreased integrity of the epidermal barrier caused by inflammation or disease of the skin, eg, excoriations, psoriasis, or severe sunburn, may increase minoxidil absorption.

Patient Information. A patient information leaflet is included with each package and in the full product information.

Drug Interactions No drug interactions are known. Theoretically, absorbed minoxidil may potentiate orthostatic hypotension in patients taking guanethidine.

Carcinogenesis, Mutagenesis, and Impairment of Fertility No carcinogenicity was found with topical application. Oral administration may be associated with an increased incidence of malignant lymphomas in female mice and hepatic nodules in male mice In rats, there was a dose-dependent reduction in conception rate.

Pregnancy Category C: ROGAINE should not be used by pregnant women.

Labor and Delivery The effects are not known.

Nursing Mothers ROGAINE should not be administered

Pediatric Use. Safety and effectiveness has not been established under age 18.

ADVERSE REACTIONS

ROGAINE was used by 3,510 patients in placebo controlled trials. Except for dermatologic events, no individual reaction or reactions grouped by body systems appeared to be increased in the minoxidil-treated patients.

Respiratory (bronchitis, upper respiratory infection, sinusitis) 5.95%, **Dermatologic** (irritant or allergic contact dermatitis) 5.27%, **Gastrointestinal** (diarrhea, nausea, vomiting) 3.42%; **Neurologic** (headache, dizziness, faintness, light-headedness) 2 56%, **Musculoskeletal** (fractures, back pain, tendinitis) 2 17%, **Cardiovascular** (edema, chest pain, blood pressure increases/decreases, palpitation, pulse rate increases/decreases) 1.28%; **Allergic** (nonspecific allergic reactions, hives, allergic rhinitis, facial swelling, and sensitivity) 1.03%, **Special Senses** (conjunctivitis, ear infections, vertigo) 0 94%; **Metabolic-Nutritional** (edema, weight gain) 0 60%, **Urinary Tract** (urinary tract infections, renal calculi, urethritis) 0.46%; **Genital Tract** (prostatitis, epididymitis) 0 46%, **Psychiatric** (anxiety, depression, fatigue) 0 28%; **Hematologic** (lymphadenopathy, thrombocytopenia) 0 23%, **Endocrine** 0.09%.

Patients have been followed for up to 5 years, and there has been no change in incidence or severity of reported reactions. Additional events, not necessarily attributed to ROGAINE use, have been reported since marketing and include: eczema, hypertrichosis, local erythema, pruritus, dry skin/scalp flaking, sexual dysfunction; visual disturbances, including decreased visual acuity, exacerbation of hair loss, and alopecia

DOSAGE AND ADMINISTRATION

Hair and scalp should be dry before application. 1 mL should be applied to the total affected areas twice daily Total daily dose should not exceed 2 mL If the fingertips are used to facilitate drug application, wash the hands afterwards.

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One 60-mL bottle with multiple applicators	NDC 0009-3367-05
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CONTINUING MEDICAL EDUCATION

(Continued from Page 22)

October 20—**Magnetic Resonance Angiography.** UCSF at Hyatt Regency Hotel, San Francisco. Sun. 7 hrs. Contact: UCSF.

October 21-25—**Clinical Magnetic Resonance Imaging.** UCSF at Hyatt Regency Hotel, San Francisco. Mon-Fri. 32 hrs. $595. Contact: UCSF.

October 26-27—**Advanced Imaging of the Musculoskeletal System.** UCSD at Hotel del Coronado, San Diego. Sat-Sun. 9 hrs. $225. Contact: Dawne Ryals, Ryals & Associates, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

October 26-27—**Vascular Ultrasound: State of the Art.** UCSF at Ritz-Carlton Hotel, San Francisco. Sat-Sun. 12 hrs. $285. Contact: UCSF.

October 28-November 1—**Sixteenth Annual Postgraduate Radiology Course.** UCSD at Hotel del Coronado, San Diego. Mon-Fri. 28.25 hrs. $550. Contact: Dawne Ryals, Ryals & Associates, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

November 1-3—**11th Annual Interventional Radiology Course.** UCSD at Hotel del Coronado, San Diego. Fri-Sun. 15 hrs. $375. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

November 4-8—**Diagnostic Radiology Seminars.** UCSF at Hyatt Regency, Maui, Hawaii. Mon-Fri. 24 hrs. $595. Contact: UCSF.

November 15-17—**Advanced Seminars in Diagnostic Imaging.** UCSD at Ritz-Carlton Hotel, Laguna Niguel. Fri-Sun. $400. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

REHABILITATIVE/THERAPEUTIC

October 5—**Antithrombotic Therapy.** UCD at Cancer Center Auditorium. Sat. 6 hrs. Contact: UCD.

November 14-16—**3rd Triennial Symposium on New Directions in Antiviral Chemotherapy.** UCSF at Sheraton Palace Hotel, San Francisco. Thurs-Sat. 19 hrs. $200. Contact: UCSF.

SURGERY

July 19—**Radiosurgery Workshop 1991.** UCLA Extension at Neurophychiatric Institute Auditorium. Fri. 7.25 hrs. $50. Contact: UCLA.

September 12-13—**Advanced Endoscopic Surgery.** UCD. Thurs-Fri. 17 hrs. $3200. Contact: UCD.

October 10-13—**Wound Management Workshop: October.** UCSD at San Diego Hilton Beach and Tennis Resort. Thurs-Sun. 18 hrs. $435. Contact: Edith Bookstein, PO Box 2586, La Jolla 92038. (619) 454-3212.

October 27-30—**Preparing for Surgery: Medical Evaluation of the Preoperative Patient.** American College of Physicians and UCD at La Playa Hotel, Carmel. Sun-Wed. Contact: ACP, Independence Mall West, 6th St at Race, Philadelphia, PA 19106-1572. (800) 523-1546, ext. 2429.

November 2-9—**13th International Seminar on Operative Arthroscopy.** UCLA at Ritz-Carlton, Mauna Lani Resort, Hawaii. 1 week. 37 hrs. $995. Contact: UCLA.

GENERAL/MULTIDISCIPLINARY

July 20-21—**HIV Update.** UCD at Cancer Center Auditorium. Sat-Sun. 13 hrs. $200. Contact: UCD.

December 9-10—**Clinical Care of the AIDS Patient.** UCSF at San Francisco Marriott Hotel. Mon-Tues. 13 hrs. $250. Contact: UCSF.

COLORADO

This listing of continuing medical education programs in Colorado is compiled by the Denver Medical Society. To list CME programs here, please send information at least two months in advance to: Mr Robert L. Kennedy, Denver Medical Society, 1850 Williams Street, Denver, CO 80218; or telephone (303) 377-1850.

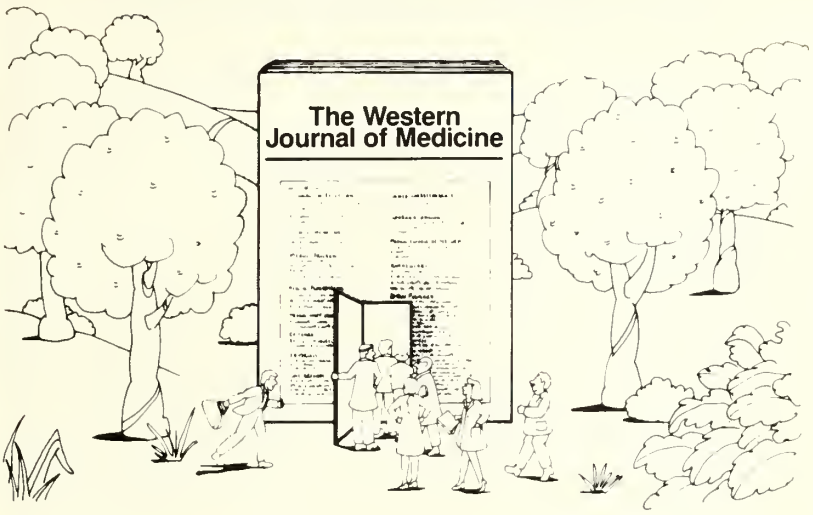
Brochures, course information, and registration forms are available from the contact person or organization.

July 22-26—**Renal Disease for the Internist and Nephrologist.** University of Colorado School of Medicine at The Given Institute, Aspen. Mon-Fri. Contact: Joann Bauer, (303) 270-5195 or (800) 882-9513.

July 25-27—**Preparing for Reform—Proposals, Assumptions and Implications for Financing American Health Care—11th Annual Montgomery Dorsey Symposium.** Presbyterian/St. Luke's Community Foundation at Vail. Thurs-Sat. Contact: Mary Pettigrew, (303) 322-3515.

(Continued on Page 90)

Inside Information



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Brief Summary of Prescribing Information

AUGMENTIN amoxicillin/clavulanate potassium

Indications and Usage: *Augmentin* is indicated in the treatment of infections caused by susceptible strains of the designated organisms in the conditions listed below

Lower Respiratory Infections caused by β-lactamase-producing strains of *Hemophilus influenzae* and *Branhamella catarrhalis*
Otitis Media caused by β-lactamase-producing strains of *Hemophilus influenzae* and *Branhamella catarrhalis*
Sinusitis caused by β-lactamase-producing strains of *Hemophilus influenzae* and *Branhamella catarrhalis*
Skin and Skin Structure Infections caused by β-lactamase-producing strains of *Staphylococcus aureus*, *E. coli*, and *Klebsiella* spp
Urinary Tract Infections caused by β-lactamase-producing strains of *E. coli*, *Klebsiella* spp and *Enterobacter* spp

While *Augmentin* is indicated only for the conditions listed above, infections caused by ampicillin-susceptible organisms are also amenable to *Augmentin* treatment due to its amoxicillin content. Therefore, mixed infections caused by ampicillin susceptible organisms and β-lactamase-producing organisms susceptible to *Augmentin* should not require the addition of another antibiotic.

Bacteriological studies, to determine the causative organisms and their susceptibility to *Augmentin*, should be performed together with any indicated surgical procedures.

Therapy may be instituted prior to obtaining the results from bacteriological and susceptibility studies to determine the causative organisms and their susceptibility to *Augmentin* when there is reason to believe the infection may involve any of the β-lactamase-producing organisms listed above. Once the results are known, therapy should be adjusted, if appropriate.

Contraindications: A history of allergic reactions to any penicillin is a contraindication.

WARNINGS: SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTOID) REACTIONS HAVE BEEN REPORTED IN PATIENTS ON PENICILLIN THERAPY. ALTHOUGH ANAPHYLAXIS IS MORE FREQUENT FOLLOWING PARENTERAL THERAPY, IT HAS OCCURRED IN PATIENTS ON ORAL PENICILLINS. THESE REACTIONS ARE MORE LIKELY TO OCCUR IN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY, AND/OR A HISTORY OF SENSITIVITY TO MULTIPLE ALLERGENS. THERE HAVE BEEN REPORTS OF INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE REACTIONS WHEN TREATED WITH CEPHALOSPORINS. BEFORE INITIATING THERAPY WITH ANY PENICILLIN, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS, OR OTHER ALLERGENS. IF AN ALLERGIC REACTION OCCURS, *AUGMENTIN* SHOULD BE DISCONTINUED AND THE APPROPRIATE THERAPY INSTITUTED. **SERIOUS ANAPHYLACTOID REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE, OXYGEN, INTRAVENOUS STEROIDS, AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED.**

Precautions General: While *Augmentin* possesses the characteristic low toxicity of the penicillin group of antibiotics, periodic assessment of organ system functions, including renal, hepatic and hematopoietic function, is advisable during prolonged therapy.

A high percentage of patients with mononucleosis who receive ampicillin develop a skin rash. Thus, ampicillin class antibiotics should not be administered to patients with mononucleosis.

The possibility of superinfections with mycotic or bacterial pathogens should be kept in mind during therapy. If superinfections occur (usually involving *Pseudomonas* or *Candida*), the drug should be discontinued and/or appropriate therapy instituted.

Drug Interactions: Probenecid decreases the renal tubular secretion of amoxicillin. Concurrent use with *Augmentin* may result in increased and prolonged blood levels of amoxicillin.

The concurrent administration of allopurinol and ampicillin increases substantially the incidence of rashes in patients receiving both drugs as compared to patients receiving ampicillin alone. It is not known whether this potentiation of ampicillin rashes is due to allopurinol or the hyperuricemia present in these patients. There are no data with *Augmentin* and allopurinol administered concurrently. *Augmentin* should not be co-administered with Antabuse® (disulfiram).

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have not been performed to evaluate carcinogenic or mutagenic potential.

Pregnancy (Category B): Reproduction studies have been performed in mice and rats at doses up to ten (10) times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to *Augmentin*. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery: Oral ampicillin class antibiotics are generally poorly absorbed during labor. Studies in guinea pigs have shown that intravenous administration of ampicillin decreased the uterine tone, frequency of contractions, height of contractions and duration of contractions. However, it is not known whether the use of *Augmentin* in humans during labor or delivery has immediate or delayed adverse effects on the fetus, prolongs the duration of labor or increases the likelihood that forceps delivery or other obstetrical intervention or resuscitation of the newborn will be necessary.

Nursing Mothers: Ampicillin class antibiotics are excreted in the milk, therefore, caution should be exercised when *Augmentin* is administered to a nursing woman.

Adverse Reactions: *Augmentin* is generally well tolerated. The majority of side effects observed in clinical trials were of a mild and transient nature and less than 3% of patients discontinued therapy because of drug-related side effects. The most frequently reported adverse effects were diarrhea/loose stools (9%), nausea (3%), skin rashes and urticaria (3%), vomiting (1%) and vaginitis (1%).

The overall incidence of side effects, and in particular diarrhea, increased with the higher recommended dose. Other less frequently reported reactions include abdominal discomfort, flatulence and headache.

The following adverse reactions have been reported for ampicillin class antibiotics:

Gastrointestinal: Diarrhea, nausea, vomiting, indigestion, gastritis, stomatitis, glossitis, black "hairy" tongue, enterocolitis and pseudomembranous colitis.

Hypersensitivity reactions: Skin rashes, urticaria, angioedema, serum sickness-like reactions (urticaria or skin rash accompanied by arthritis/arthralgia, myalgia and frequently fever), erythema multiforme (rarely Stevens-Johnson Syndrome), and an occasional case of exfoliative dermatitis have been reported. These reactions may be controlled with antihistamines and, if necessary, systemic corticosteroids. Whenever such reactions occur, the drug should be discontinued, unless the opinion of the physician dictates otherwise. Serious and occasional fatal hypersensitivity (anaphylactic) reactions can occur with oral penicillin (See Warnings).

Liver: A moderate rise in SGOT, SGPT, AST, and/or ALT has been noted in patients treated with ampicillin class antibiotics including *Augmentin*. The significance of these findings is unknown. As with some other penicillins and some cephalosporins, hepatic dysfunction has been reported rarely, with the predominant effects being cholestatic, hepatocellular, or mixed cholestatic-hepatocellular. Signs/symptoms may appear during or after therapy and they resolve completely over time.

Hemic and Lymphatic Systems: Anemia, thrombocytopenia, thrombocytopenic purpura, eosinophilia, leukopenia and agranulocytosis have been reported during therapy with penicillins. These reactions are usually reversible on discontinuation of therapy and are believed to be hypersensitivity phenomena. A slight thrombocytosis was noted in less than 1% of the patients treated with *Augmentin*.

Central Nervous System: Reversible hyperactivity, agitation, anxiety, insomnia, confusion, behavioral changes, and/or dizziness have been reported rarely.

Dosage Adults: The usual adult dose is one *Augmentin* '250' tablet every eight hours. For more severe infections and infections of the respiratory tract, the dose should be one *Augmentin* '500' tablet every eight hours.

Since both the *Augmentin* '250' and '500' tablets contain the same amount of clavulanic acid (125 mg, as the potassium salt), two *Augmentin* '250' tablets are not equivalent to one *Augmentin* '500' tablet. Therefore, two *Augmentin* '250' tablets should not be substituted for one *Augmentin* '500' tablet for treatment of more severe infections.

Children: The usual dose is 20 mg/kg/day, based on amoxicillin component, in divided doses every eight hours. For otitis media, sinusitis and other more severe infections, the dose should be 40 mg/kg/day, based on the amoxicillin component, in divided doses every eight hours. Also available as *Augmentin* '125' and '250' chewable tablets.

Children weighing 40 kg and more should be dosed according to the adult recommendations.

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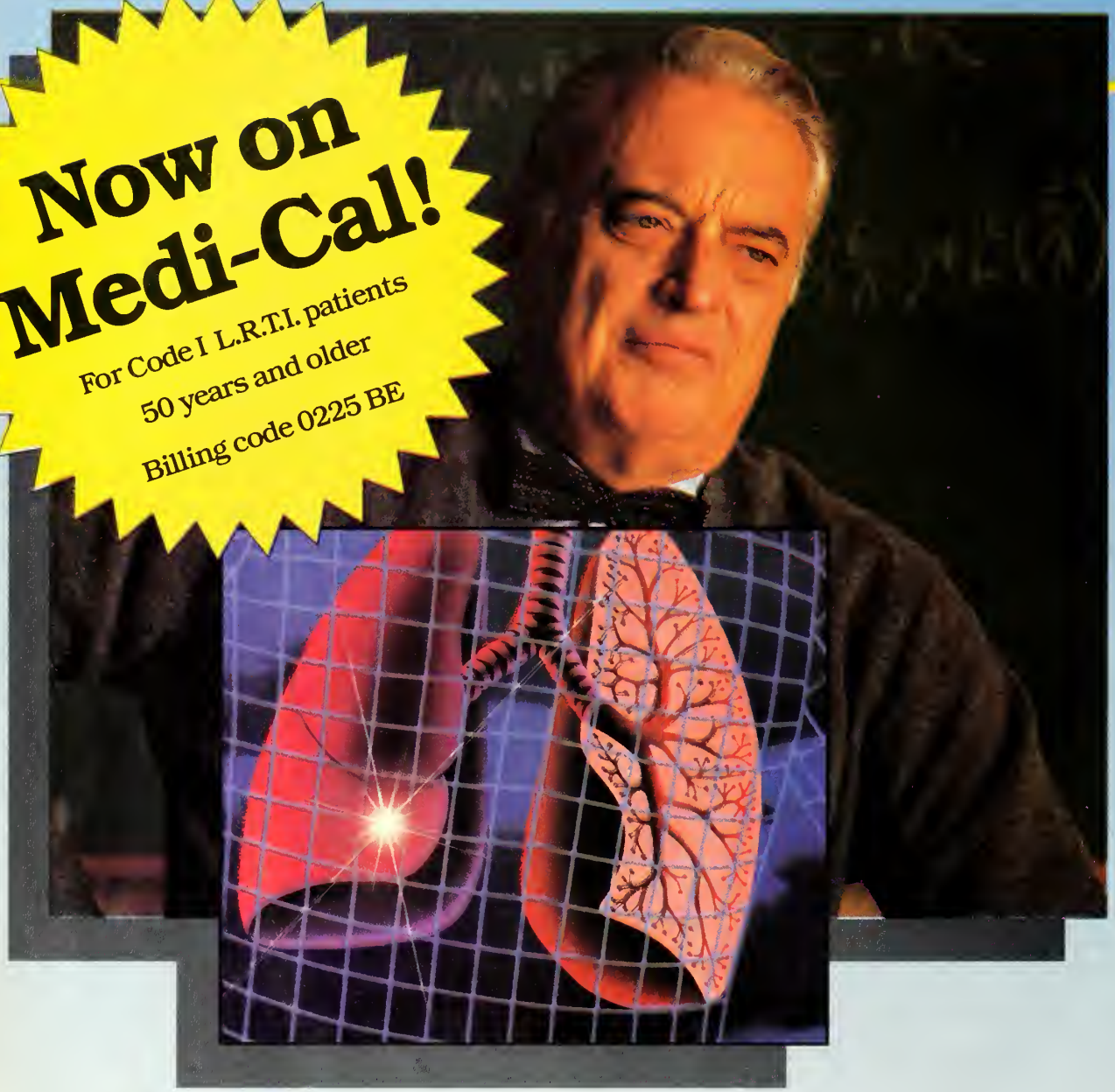

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Articles

The Health Status of Minority Populations in the United States

HERBERT W. NICKENS, MD, MA, *Washington, DC*

There is increasing national recognition that while our nation's health care system is the most expensive in the world, the health care status of Americans overall ranks poorly compared with other Western, industrialized nations. In the United States we tend to look at minority-majority variations of health status, as well as the variations of many other indicators by race or ethnicity, because race and ethnicity are particularly important components of our society. In general, health status indicators of minority Americans are worse than those of whites. In some locales, death rates of minority Americans are comparable to those of Third World nations. At the same time, minority Americans make up a rapidly increasing proportion of the nation's population and work force. Our baseline national data on some minority groups, however, currently are inadequate to detect shifts in health status. Finally, the rapidly expanding problem of the acquired immunodeficiency syndrome among some minority populations provides both an imperative and an opportunity to learn how model prevention programs should be designed and executed.

(Nickens HW: The health status of minority populations in the United States. West J Med 1991 Jul; 155:27-32)

Racial and ethnic minorities in the American context denote those that are a small proportion of the overall population; are socioeconomically disadvantaged; have a history of past discrimination in the United States; and are people of color, that is, not European, not white. Despite the history of discrimination and oppression against those of European origins such as Irish Americans, there persists a particular intensity about caste status associated with "colored" minorities.

While a detailed discussion of the history of each US minority group is far beyond the scope of this article, each group and subgroup has associated historical variations on the above five characteristics. There are also variations by geographic location within the United States. For example, the status of and the prejudices against African Americans have different characteristics than those against Mexican Americans, and the biases against the latter group are much more intense in certain areas of the Southwest than in other parts of the country.

It is only because of the intense national emotional investment—positive and negative—in matters related to our minority populations that a treatment of minority health has meaning. Were our nation not already attuned to divisions into minority and majority, it might make more sense to analyze health status using other independent variables such as socioeconomic status, with racial and ethnic variables occupying a more secondary status. In that case, our health surveillance systems also would be programmed to gather data by income, education, and occupation, and race could be of more peripheral interest.

The central point is that minority status is overwhelmingly a part of our social and cultural system and our history; the fact that health status varies by race is also a consequence of our social and cultural system and history. The genetic factors in minority health are negligible. Unfortunately, there is also a long and checkered history associated with the use of "inherent" inferiority serving as a justification for the inferior status attributed to a wide variety of groups, including American white immigrant groups. Often this genetic inferiority has been imputed to affect intelligence or moral elevation. Once again, this misuse of genetics has been in the service of contemporary social, economic, or cultural purposes.

With regard to minority health, the evidence suggests that the contribution of genetic susceptibility to minority health disparities is relatively small. The genetic cause of sickle cell disease is clear, but sickle cell disease is not a major contributor to mortality rates among African Americans. Hypertension among African Americans and non-insulin-dependent diabetes mellitus among Latinos and Native Americans probably do have a genetic component. Even in these last examples, however, where there may be a genetic predisposition, the development of disease is far from inevitable. Moreover, many minority populations have mixed with other groups. African Americans, for example, have historically been rigidly categorized as such, despite clear phenotypic evidence of commingling between African Americans and whites. Therefore, genetic screening and counseling do not offer much promise for improving minority health status and carry the stigma of eugenics.

There is another political aspect of minority health status. The health status of minorities varies widely, both within and among groups. While it might seem logical that those with better health status would find this good news, in fact, it often is perceived as possible evidence that a particular group does not need assistance. This is particularly true for groups whose health status may be relatively good but whose other indices of well-being such as educational attainment or income may show considerable disadvantage.

Minority Health Status

There are four generally recognized minority groups in the United States: Asians and Pacific Islanders, African Americans, Latinos, and Native Americans. While these

From the Division of Minority Health, Disease Prevention/Health Promotion, Association of American Medical Colleges, Washington, DC.

Reprint requests to Herbert W. Nickens, MD, MA, Vice President for Minority Health, Disease Prevention/Health Promotion, Association of American Medical Colleges, One Dupont Circle NW, Washington, DC 20036.

ABBREVIATIONS USED IN TEXT

AIDS = acquired immunodeficiency syndrome
DHHS = [US] Department of Health and Human Services
HIV = human immunodeficiency virus
NIH = National Institutes of Health

four groups combined constitute about one of five Americans, their population growth is substantially greater than that of whites. It is estimated that by year 2020 about 40% of school-aged Americans will be minority children.[1,2] The term "minority" falsely suggests a homogeneous group of nonwhites. The reality is extraordinary diversity both within and among minority groups that resists parsimonious categorizations. In certain locales such as California and New York City, well-developed racial and ethnic communities make this diversity apparent.

It has long been known that the health status of African Americans in the United States is much worse than that of whites. This was documented at least as far back as 1906 by W.E.B. DuBois in his report, *The Health and Physique of the Negro American.*[3] There have been occasional studies since DuBois's that reported the disparity between African-American and white health statuses in America, and the federal government's statistical reports have for many years divided health data into nonwhite (the vast majority of which historically were African American) and white, and more recently into either black, white, and other, or black, non-Hispanic white, and Hispanic.

The 1985 Report of the US Department of Health and Human Services (DHHS) Secretary's Task Force on Black and Minority Health was a landmark document. The Secretary's Task Force Report was distinctive from previous reports in these ways:

- It focused on all four of the major minority groups in the United States as well as the white population, in keeping with the increasing racial and ethnic diversity of the United States;
- It was prepared under the aegis of the National Institutes of Health (NIH) and drew its chair and much of its staff from that federal body;
- It used the somewhat more dramatic statistical presentation of "excess deaths" rather than the usual comparison of death rates, bringing home the message that these were lives lost that would not have been lost had minority death rates been the same as those of the white population;
- It was launched by a DHHS secretary in a conservative Republican administration, thus acquiring a legitimacy that would be less likely if either a nonfederal sponsor or a more liberal administration had commissioned the study;
- The report's sheer weight (about 3,000 pages) and its thoughtful analysis of the various causes of death established a new high-water mark for academic rigor brought to bear on minority health issues and introduced more forcefully than ever the issues of health promotion and disease prevention into strategies about the health of these populations; and
- The thrust of the report was such that a highly visible Office of Minority Health was created in DHHS to advocate for and oversee the implementation of the task force's recommendations.

TABLE 1.—*Net Excess Deaths by Minority Group**

Variable	*African Americans No. (%)*	*Latinos No. (%)*	*Native Americans No. (%)*	*Asians No. (%)*
US Population, No. (%)† . . .	26.1 (11.5)†	14.5 (6.5)†	1.5 (<1)†	3.7 (1.6)†
Excess deaths, No. (%)	58,942 (42)	≈7,000‡ (10)	1,042 (22)	−819 (14)

*From US Department of Health and Human Services.[5] Excess deaths are calculated as an average of the years 1979 to 1981. Excess deaths = the number of deaths actually observed before age 70 minus the number of deaths that would be predicted when age- and sex-specific death rates of the US white population are applied to the minority population.

†1980 United States census population, in millions.

‡These are rough estimates made from Texas-surname data, and Mexican/Cuban-born data. They are provided to give some idea of the order of magnitude of excess deaths in Latino populations.

Demographics and Health Status of Minority Populations

Some of the mortality rates and other health-related data presented in this article are drawn from the task force's report; all of the excess death calculations are from that source. The data from the task force are in some cases a decade old. It is regrettable that while the report did stimulate greater awareness of the importance of information on minority Americans, that interest has only partially been reflected in data collection policies and funding levels. Data on minorities other than African Americans are still unacceptably sparse. The task force data on non-African-American minorities were generated from special data runs and analyses that were commissioned. The data from the task force will be used here only to sketch broad patterns of mortality and morbidity and the relative health status among minority and majority populations. All indications are that, with the exception of the acquired immunodeficiency syndrome, these have changed little. While it is true that the crack cocaine epidemic has effected a qualitative and quantitative intensification of urban drug abuse, its effects on mortality have been insubstantial and indirect. Indirectly, crack cocaine use has also contributed to increased homicide rates (discussed later) and plays an increasing role in human immunodeficiency virus (HIV) transmission, particularly because of the exchange of sex for drugs. There is no doubt that crack cocaine use has also caused substantial morbidity because of its erosion of the social fabric through the disintegration of families and corruption due to the profits of the drug business.

Asians and Pacific Islanders. Asians and Pacific Islanders are currently the fastest-growing population in the United States, with an increase in population of 141% from 1970 to 1980 compared with an increase of 17% for African Americans, 39% for Latinos, and 12% for the overall population.[4] Asian and Pacific Islander populations are heterogeneous. They include well-established Asian-American populations that are more likely to be born in the United States, such as Japanese and to a lesser extent Chinese and Filipinos. Asian-American populations of Japanese, Chinese, and Filipino origins are of similar size and together constitute three of five Asian Americans. The balance of Asian Americans are approximately evenly divided among those of Asian-Indian, Korean, and Southeast Asian origins; a large number of Southeast Asians have immigrated to the United States as a result of the Vietnam War. The median family income for Asians and Pacific Islanders is higher than that for other minority groups and whites,[4] although this figure may be artificially inflated because of a larger number of workers per household. As calculated in the Secretary's Task Force Re-

port, the excess death rate of Asians and Pacific Islanders was −14% (see Table 1 for all excess death rates).[5] This means that in the aggregate, Asians and Pacific Islanders have lower mortality rates than does the white population.

There are subgroups of Asians and Pacific Islanders, however, that have considerable socioeconomic and health problems, particularly the newly arrived refugee and immigrant populations from Southeast Asia. For example, the Vietnamese have an average family income that is about half that of the Asian and Pacific Islander population as a whole. Southeast Asians have high rates of diseases associated with poverty, such as tuberculosis. Surges in the national tuberculosis incidence have been linked to a sudden influx of refugees from Kampuchea, Laos, and Vietnam. These groups also account for Asians and Pacific Islanders having the highest rate of tuberculosis of any racial or ethnic group in the United States. The trend for tuberculosis among Asians and Pacific Islanders, however, is down (along with that for Native Americans and whites) but that for African Americans and Latinos is up, probably due to the HIV-tuberculosis connection in the last two groups.[6]

African Americans. African Americans are currently the largest minority group in the United States. Diversity within African Americans is less overt than among other minority groups because of the homogenizing effect of the long-standing African-American presence in America, with less contribution from recent immigration compared with that of Asians or Latinos. Approximately a third of African Americans live below the poverty level, and unemployment among African Americans has been about twice that of whites for at least the past 50 years. On the other hand, the African-American middle class has increased substantially in the past 15 years.

Mortality rates among African Americans are higher than those of the other three minority groups or whites. They are about 50% higher than those for whites, and the excess death rate calculated in the task force's report was 42%.[5,7] It is even more disturbing that since the task force's report, life-expectancy rates for African Americans and whites have been diverging: those for blacks in 1985 and 1986 actually decreased and were unchanged for 1987, and those for whites increased for those years.[7] A recalculation of the excess death rate using these data would, therefore, show an increase. It is too soon to know whether these data portend a longer term trend of divergence between African-American and white mortality rates; clearly they indicate that the gap is not closing. The ratio of black-to-white death rates for the past 40 years (Figure 1) shows no impressive improvement, though African-American women do display some gains relative to white women. Infant mortality rates, often seen as a key indicator of overall well-being, have in the past 40 years decreased much more rapidly for whites than for African Americans: African-American rates were 164% of those for whites in 1950, 208% by 1987.[7]

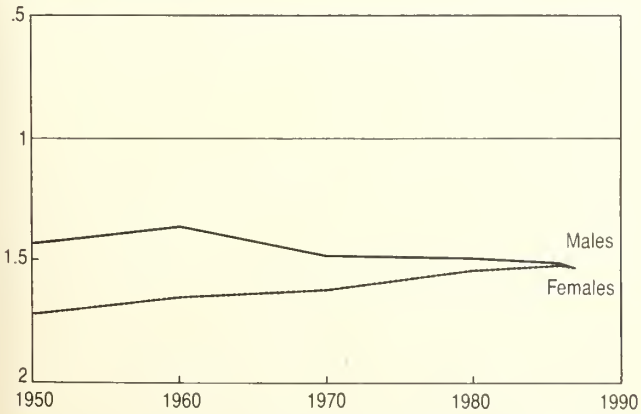

Figure 1.—The ratio of African American-to-white death rates for all causes, 1950 to 1987, is shown.

Latinos. Latinos are the second largest minority in the United States. As with Asian Americans, Latinos come from different countries of origin. Three fifths of Latinos are Mexican in origin, about 15% are from Puerto Rico, 6% from Cuba, and the rest from Central America, South America, and from other Hispanic origins.[8] Latinos also are diverse with regard to socioeconomic status measures, circumstances under which they came to the United States, and levels of acculturation.

Complete national vital statistics for Latinos are currently unavailable because "Latino" is not a racial category, and data on Latinos are gathered by some states or cities but not others. As reflected in available mortality rates, however, the health status of Latinos in the aggregate appears to be remarkably good, much more similar to that of the white population, and much better than for the African-American population. This overall conclusion is supported by recently published data[9] and by a number of studies: the task force studied death rates of three different Latino populations (US Cuban- and Mexican-born citizens, and Texas Spanish surname); a review of studies on Southwestern Latinos, most of whom were Mexican American[10]; and a review of mortality rates of Mexican Americans and Puerto Ricans in Chicago.[11] An additional feature raised by the last study is the implication that Puerto Rican health status is worse than that of Mexican Americans though still better than that of African Americans.

Because the overall health status of Latino populations is remarkably good, despite the fact that the overall poverty rates of Latinos and African Americans are similar, Latino health status has been dubbed an "epidemiologic paradox."[10] Because of the lack of national data, the task force could not calculate a national excess death rate for Latinos. For the three Latino populations described earlier for which the task force gathered data, the excess death rates were 2.2%, 7.2%, and 14%, respectively. To begin to answer many of the research questions raised by the "paradoxical" nature of Latino health status, it will be important not only that national data be collected but that the data be broken out for the major subgroups within the Latino population.

Native Americans. Native Americans are the smallest and perhaps most diverse of all American minority groups. About 1.6 million Native Americans are distributed among almost 500 tribes and village units. Overall, Native-American poverty rates are similar to those of Latinos and African Americans. Native Americans had the second worst excess death rates of any of the minority groups and whites. Their excess death rate was 22%, and 87% of those excess deaths occurred before age 45, with relatively low death rates from chronic diseases except for diabetes mellitus. Among many tribes, alcohol abuse, suicide, and high death rates from unintentional injuries and interpersonal violence decimate the young Native-American population.

Patterns of Mortality

Six categories of diseases cause the overwhelming major-

TABLE 2.—*Causes of Death Patterns of Minority Groups**

Disease/Problem	Death Rate Higher Than Whites: African Americans	Latinos	Native Americans	Asian/ Pacific Islanders
Cancer	X	...	...	...
Cardiovascular disease	X	...	...	...
Chemical dependency	X	X	X	...
Diabetes mellitus	X	X	X	...
Infant mortality	X	...	X	...
Violence	X	X	X	...
Homicide	X	X	X	...
Suicide	...	...	...	...
Unintentional injury	X	X	X	...
AIDS/HIV disease	X	X	...	...

AIDS = acquired immunodeficiency syndrome; HIV = human immunodeficiency virus

*From the US Department of Health and Human Services.[5,7,9]

ity of excess deaths in minority populations: cancer, cardiovascular disease, chemical dependency (measured by deaths due to cirrhosis), diabetes mellitus, infant mortality, and violence. The relative importance of these six varies from group to group (Table 2). The most important contributor to the health status differential between African Americans and the other minority populations is the fact that only African-American populations suffer excess deaths from cardiovascular disease and cancer, the leading causes of death in America.

The causes for African Americans' higher rates of cancer and cardiovascular disease as compared with whites are not completely understood. The higher smoking rate of African-American men is certainly important; smoking among minorities will be discussed later. A second important factor is the higher prevalence of hypertension among African Americans. Despite some improvement, African-American adults still have a higher prevalence of hypertension than whites; African-American men have levels somewhat higher than those of white men, and the levels of African-American women are similar to those of African-American men, a prevalence 50% higher than that of white women.[7]

Issues for Special Consideration in Minority Health Status

Acquired Immunodeficiency Syndrome (AIDS)

Since the task force report, AIDS has become an increasingly important cause of death in the United States. The cumulative prevalence rates of AIDS among African Americans and Latinos are approximately three times those for whites. Native Americans and Asians and Pacific Islanders have thus far not shown rates of AIDS in excess of those among white Americans. Homosexual-bisexual men still account for most reported new AIDS cases, but rates of increase of new AIDS cases due to homosexual or bisexual transmission are lower than the rates of increase of transmission among intravenous drug users, their sexual partners, and their children.[12] As has been the case since the beginning of the epidemic, these last HIV transmission patterns are ones in which African Americans and Latinos predominate. This has two implications that need to be highlighted:

- Because AIDS statistics are usually given with all cases reported since the epidemic began in 1981 as the denominator, emerging trends are not obvious. African Americans and Latinos, however, represented 25% and 14%, respectively, of the first 25,000 cases of AIDS (through September 1986)[13] but 32% and 17%, respectively, of the approximately 24,000 cases reported in the first six months of 1990.[14] Therefore, it is virtually certain that the proportion of persons with AIDS who are minority will increase in the future, becoming more than half of new cases in the 1990s.
- Among African Americans and Latinos, AIDS is a disease afflicting a substantial number of men, women, and their children, thus attacking the family unit, already a beleaguered institution in both groups because of high rates of separation, divorce, and children born to single women. Moreover, many of these same men and women are also plagued by intravenous drug or crack use. In many cities an increasing number of children are being abandoned or orphaned by mothers and fathers who are dead or dying of HIV infection or rendered dysfunctional by drug abuse.

Homicide

African-American homicide rates for many decades have been several times those for whites. African Americans' ratios of homicide rates are currently 7.0 and 4.2 times those for white men and women, respectively.[7] The data available indicate that rates of homicide for Latinos and Native Americans are in between those for African Americans and whites.[5,15] In general, within any population, homicide rates for men are much higher than those for women, and homicide rates for American whites are several times higher than those of other industrialized nations.

Historically, homicides typically occurred among young people in their teens and 20s, with the victim and assailant acquainted, where one or both of the parties had ingested alcohol or other drugs, with the homicide arising out of an argument, and the principal weapon being a firearm. In recent years, urban warfare using automatic weapons waged over turf and the control of illicit drug distribution has added a new element to this pattern. Fluctuations in the number of homicides occur in part because of the rise and fall of the proportion and number of young people in the population. In the next few years, the number of homicides may rise precipitously, above the post-World War II peak of 24,278[16] in 1980, because of the "baby boomlet" combined with urban drug- and gang-related conflict.

Homicide and interpersonal violence increasingly are being redefined as a public health rather than a criminal justice problem. Unlike many other important causes of mortality and morbidity, however, homicide and violence are overwhelmingly caused by social and psychological forces and carry substantial stigma and dread, making dispassionate assessment or intervention very difficult. This stigma is the result of several factors:

- Our society is intensely ambivalent about violence, viewing it as just and heroic in some contexts but abhorrent and primitive in others;
- Historically, violent revolts on the part of Native Americans, African Americans, and (at certain points in American history) Latinos have been a source of intense dread and danger for European Americans;
- There is a long-standing association of high rates of homicide with minority Americans, particularly African Americans; and
- Homicide victims and perpetrators are overwhelm-

ingly of the same race, which when combined with the higher rates among minorities, adds an element of self-destructiveness.

This issue of stigma is also reflected in the long-standing debate about the etiology of high homicide rates for African Americans. Possible causes range from a purported "subculture of violence" to hypotheses in which the effects of poverty and societal racism are given primacy.[17] While intellectually the two ends of this causal spectrum are not inherently mutually exclusive, the proponents for and the context in which these two categories of explanations are raised tend to be. Unfortunately, discussions about etiology too often contain strong elements of debating the question, "Whose fault is this, really?" Thus, despite the fact that homicide and interpersonal violence are increasingly seen as public health problems and, therefore, amenable to prevention, because of the sensitivity of this topic, progress to develop and evaluate model prevention programs has been slow. More vigorous development of programs must take place, but because of the considerations mentioned, scrupulous attention must be paid to community sensitivities when violence prevention programs are designed.

Tobacco

Tobacco has been identified as the most preventable cause of mortality in our country. African-American and Latino men have substantially higher smoking rates than white men (about 40% versus 30%, respectively).[7,18] African-American women smoke at rates similar to those of white women, while Latino women smoke at lower rates. Asian and Native American data are less complete. What gives smoking particularly sinister overtones is the targeting of minorities by tobacco companies for special marketing attention.[19] This takes the form of large numbers of billboards in minority communities, advertisements in ethnic publications, and support of African-American and Latino cultural events and organizations. The US Secretary of Health and Human Services publicly criticized R.J. Reynolds for its planned introduction of Uptown, a brand of cigarettes that admittedly was targeted toward African Americans; Uptown was withdrawn. Tobacco particularly is singled out for this kind of critcism because it is probably the only legal product that is a serious health hazard even when used as intended. Because of the decades-long lag time between initiation of smoking and onset of disease, the current high smoking rates among Latino men, combined with apparently low current rates of lung cancer and other smoking-related disorders, offer a clear opportunity and imperative to intervene.

Poverty

Throughout history, lower socioeconomic status has been associated with higher rates of mortality. Socioeconomic status tends to be measured by some combination of occupation, income, and educational attainment. On all three of these indices minorities tend to be of lower socioeconomic status than whites. In general, minorities have substantially lower incomes than whites. In 1987 the poverty rate was 33.1% for African Americans and 28.2% for Latinos, compared with 10.5% for whites.[20] Income is an important determinant of socioeconomic status, and socioeconomic status is a powerful variable in health and behavior patterns.[21] In general, minorities have lower levels of educational attainment than whites.[22] For example, higher rates of risky health behaviors such as cigarette smoking correlate inversely with education and hence with socioeconomic status.[23]

Adverse health indicators may correlate inversely with socioeconomic status, but it is not always possible to disentangle the effects of occupation, income, and education. In addition to its relationship with socioeconomic status, lower educational attainment has other direct implications for health. For example, lower educational attainment decreases the ability to comprehend written information and instructions from physicians, health care facilities, third-party payers, and on medications. Since a great deal of our health care system is organized around the assumption of literacy in English, many minority populations cannot effectively gain access to and use health care.

Despite the importance of socioeconomic status on health status, when the relative health status of minority populations is examined, it does not simply correlate with their socioeconomic status. Socioeconomic status may operate in minority populations with a time component. It may be that populations that have been poor in the United States over several generations without substantial progress up the socioeconomic ladder, suffering continual discrimination and frustration, are likely to feel much more powerless and will have a very different perception of their lot than newly arrived immigrants who are poor but still hopeful. There is evidence that southern California Latino women have poorer birth outcomes after they become more acculturated.[24]

Health Insurance

Having health insurance is an important factor in health status, but about half of African Americans and Latinos under 65 are uninsured or are covered by Medicaid versus about one in five whites. The proportion of all Americans under 65 who are uninsured has increased in the decade between 1977 and 1987; African Americans and Latinos accounted for 50% of that increase. Of those under 65, 15% of whites, 25% of African Americans, and 35% of Latinos are uninsured.[25] Minorities are disproportionately uninsured because the United States has no national system of health insurance that would "level the playing field" so that all socioeconomic levels of the population possess a means to pay for care. While there are high-income persons who lack health insurance, uninsured persons in our society are overwhelmingly low-income, whether employed or not. Moreover, minorities are also dramatically overrepresented among those on Medicaid. It is now well understood that Medicaid probably provides inadequate access to inpatient care.[26] Medicaid reimbursement is also particularly low for outpatient care, which is essential for the best management of the chronic diseases that are the major killers of all Americans and is increasingly essential for management of the spectrum of HIV-related diseases.

Comment

At the outset I asserted that the topic of minority health has moment because of the intensity and persistence of the conflicts in American society regarding our nation's minority populations of color. If this formulation is true, then minority health will also remain a "hot" topic until preoccupation with race diminishes or the health status of minority populations comes to parity with that of whites. Neither of these seems likely.

If anything, overt racial conflicts have increased in the United States. Moreover, current trends do not suggest that overall minority-majority health status gaps are closing. For the foreseeable future, therefore, minority health will continue to be an arena of struggle and conflict that will contain elements of public health and medical science on the one hand but group striving and politics on the other.

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Articles

Fine Needle Aspiration Biopsy of Superficial Masses in Children

LYDIA PLEOTIS HOWELL, MD; LIISA A. RUSSELL, MD; P. HOLBROOK HOWARD, MD; *and* RAYMOND L. TEPLITZ, MD, *Sacramento, California*

Fine needle aspiration biopsy (FNAB) is an underused diagnostic procedure in children, particularly in the evaluation of superficial masses. A total of 54 FNABs of superficial masses were performed in children aged 1 month to 15 years. Adequate material for diagnosis was obtained in 50 attempts. The cytologic diagnosis increased clinical understanding and provided a guide for treatment in 46 of the 50 cases. The cytologic diagnosis was confirmed in 15 of 19 patients who underwent an operation. Surgical intervention was obviated in 31 patients. There was one false-positive diagnosis of cancer. We describe the role of FNAB in children and its technique, accuracy, and diagnostic problems.

(Howell LP, Russell LA, Howard PH, Teplitz RL: Fine needle aspiration biopsy of superficial masses in children. West J Med 1991 Jul; 155:33-38)

Fine needle aspiration biopsy (FNAB) has become a widely accepted procedure employed by a variety of medical specialists in the evaluation and management of deep and superficial masses. In this country, however, the procedure has been used chiefly for adults. The level of experience with FNAB in a pediatric context in the United States parallels that in adults 15 to 20 years ago, when FNAB was first gaining acceptance. Although the authors of several reports have tried to popularize FNAB as a diagnostic tool in children,[1-6] pediatric physicians remain largely unfamiliar with the indications for the procedure, how it is done, and its role in clinical problem solving. We report a series of 54 FNABs of superficial masses in children younger than 16 years to familiarize those who treat the pediatric population with this diagnostic method and to demonstrate its utility and accuracy.

Materials and Methods

A total of 54 FNABs were performed on superficial masses in 51 patients ranging in age from 1 month to 15 years. Most of these were done on patients in ambulatory clinics.

The biopsy procedure was performed using a 22- to 25-gauge needle attached to a 10-ml syringe in a pistol-grip syringe holder. The use of local anesthesia at the site was optional. At least two separate passes were made on each mass. Smears were prepared on clean, unfrosted glass slides and either fixed with a commercial spray fixative or 95% ethanol, or air dried. The slides were then stained by a modified Papanicolaou or Wright-Giemsa stain. In most cases, at least one slide was evaluated at the time of the aspiration following air drying and rapid Wright-Giemsa staining or, alternatively, immediately stained with toluidine blue in a 50% ethanol solution. The latter group of slides was later stained permanently by the Papanicolaou method. If desired, needles from additional passes were rinsed directly into media for bacterial or fungal cultures, into RPMI culture medium for special studies, or into fixative for cell block preparation. Immunoperoxidase staining was done on cell blocks from the aspirate following the method described by Hsu and co-workers.[7]

Results

The anatomic sites from which aspiration biopsy specimens were taken are listed in Table 1. More than two thirds of the biopsy specimens were from the head and neck region. Of the 54 masses, 34 were persistently enlarged lymph nodes. Indications for FNAB are listed in Table 2. In 24 cases, FNAB was done to evaluate recurrence of a previously diagnosed condition; 21 of these were in patients with a history of cancer. An unsuspected second primary malignant tumor was found in one of these patients.

Adequate material for cytologic evaluation was obtained in 50 cases. Cytologic diagnoses and follow-up information are listed in Tables 3 and 4. In 46 of 50 cases, FNAB provided an increased understanding of the clinical situation and a guide to appropriate treatment. In all, 19 patients ultimately

TABLE 1.—*Anatomic Distribution of Aspirated Sites*

Location	*No.*
Head and Neck	
Cervical	21
Submandibular	3
Submental	1
Parotid	4
Periorbital	1
Preauricular	2
Thyroid	3
	35
Arm	2
Inguinal	2
Breast	3
Supraclavicular	2
Chest	3
Abdomen	1
Antecubital	1
Testis	1
Epitrochlear	2
Leg	2
	19

From the Department of Pathology, University of California, Davis, Medical Center, Sacramento.
Reprint requests to Lydia P. Howell, MD, Department of Pathology, University of California, Davis, Medical Center, 2315 Stockton Blvd, Sacramento, CA 95817.

TABLE 2.—*Clinical Indications Prompting Fine Needle Aspiration Biopsy (FNAB) and Subsequent Cytologic Diagnoses*

Clinical Indication for FNAB	*Cytologic Diagnosis (No.)*
Persistent mass with history of malignancy	Malignant recurrence (14); papillary carcinoma, thyroid (2nd primary tumor) (1); benign salivary gland tissue (1); fungus infection (1); abscess (2); hyperplasia, breast (1); unsatisfactory (1)
Persistent mass with history of medical condition other than malignancy	Consistent with atypical immune response (1); cystic hygroma fluid (1); unsatisfactory (1)
Persistent lymphadenopathy after antibiotic therapy	Granulomatous inflammation (2); cat-scratch disease (3); branchial cleft cyst (2); lymphoid hyperplasia (5); unsatisfactory (1)
Persistent lymphadenopathy, no previous antibiotic therapy	Hodgkin's disease (1); true histiocytic lymphoma (1); lymphoid hyperplasia (2); unsatisfactory (1)
Persistent mass other than lymph node	Abscess (3); granulomatous inflammation (2); gynecomastia (2); hematoma (1); benign mesenchymal tumor (1); eosinophilic granuloma (2); branchial cleft cyst (1); papillary carcinoma, thyroid (1)

underwent surgical treatment, and the cytologic diagnoses were confirmed in 15. The 2 other patients had cystic lesions that had been diagnosed cytologically as branchial cleft cysts; histologic sections from both, however, revealed cystic necrosis of a lymph node with granulomatous inflammation. No organisms were identified in either case.

One false-positive diagnosis of cancer resulted (case 3). There was also one false-negative diagnosis. A patient with a history of extranodal lymphoma presented with a persistently enlarged lymph node while on chemotherapy. The FNAB was interpreted as reactive with fibrosis. There was insufficient material obtained for flow cytometry. The node was surgically excised and revealed lymphoma.

The results of FNAB obviated surgical procedures in 31 cases. On the basis of the cytologic diagnosis, either definitive treatment was initiated or, in some cases, no treatment was considered necessary and the aspirated mass resolved spontaneously. The biopsy was considered unsatisfactory in four cases. Inadequate cellularity was noted from masses in the inguinal, epitrochlear, and cervical areas. Three of these biopsies were performed in patients who were difficult to restrain; all three masses resolved, two following antibiotic therapy. In the fourth patient, who had leukemia, the aspirate was extremely bloody and it was unclear whether the blasts seen originated from the aspirated node or represented contamination by peripheral blood. Chemotherapy was initiated.

The following cases serve as examples of the usefulness of FNAB and illustrate possible diagnostic problems.

Case 1

The patient, a 9-year-old girl, was noted to have a 4-cm by 2-cm mass located almost directly beneath and slightly posterior to the inferior portion of the sternocleidomastoid muscle on the left side of the neck. The patient had a previous history of a mediastinal mass at age 3 years. At that time, because of the urgency of the patient's medical condition (which required immediate treatment), a tissue diagnosis of that mass was never obtained and she was treated empirically for a non-Hodgkin's lymphoma with chemotherapy and mediastinal radiation therapy. The mass responded rapidly, and the patient had been well and without recurrence since that time.

A fine needle aspiration biopsy of the neck mass was done. Smears revealed a highly cellular aspirate composed of small dyshesive clusters of cuboidal or low columnar cells that showed mild to moderate anisonucleosis, nuclear hyperchromatism, and pleomorphism consistent with carcinoma. Because of the presence of occasional papillae, acinarlike structures, and intranuclear grooves and vacuoles, metastatic papillary carcinoma of the thyroid was considered (Figure 1-A). Immunoperoxidase staining for thyroglobulin was positive. There was no staining for leukocyte common antigen and only slight positivity for epithelial membrane antigen and carcinoembryonic antigen.

Following the diagnosis, a careful physical examination of the thyroid revealed an asymmetric enlargement of the left lobe. A thyroid scan showed a cold nodule in the left lobe, which was later surgically excised. The tumor measured 3

TABLE 3.—*Benign Cytologic Diagnoses With Histologic and Clinical Follow-up*

Cytologic Diagnosis	*Histologic and Clinical Follow-up (No.)*
Inflammatory	
Lymphoid hyperplasia	No biopsy: spontaneous resolution (7); biopsy: lymphoma (1)
Granulomatous inflammation	Biopsy: giant cell reparative granuloma (1), granulomatous inflammation with culture positive for *Mycobacterium tuberculosis* (1), granulomatous inflammation with culture negative for *M tuberculosis* (2)
Cat-scratch disease	Biopsy: cat-scratch disease (1); no biopsy: spontaneous resolution (2)
Abscess	Biopsy: abscess (2); no biopsy: treatment initiated (3)
Fungus infection	No biopsy: treatment initiated (1)
Hematoma	No biopsy: spontaneous resolution (1)
Benign mesenchymal tumor	Biopsy: hemangioma, parotid (1)
Gynecomastia	No biopsy: spontaneous resolution (2)
Hyperplasia, breast	No biopsy (1)
Branchial cleft cyst	Biopsy: granulomatous inflammation with cystic necrosis and culture negative for *M tuberculosis* (2); no biopsy (1)
Atypical hyperplasia consistent with history of atypical immune response	No biopsy
Benign-appearing salivary glandular tissue	No biopsy (1)
25-ml cyst fluid consistent with recurrent cystic hygroma	Surgical repair (1)

TABLE 4.—*Malignant Cytologic Diagnoses With Histologic and Clinical Follow-up*

Cytologic Diagnosis	*Histologic and Clinical Follow-up (No.)*
Carcinoma	
Papillary carcinoma, thyroid	Thyroidectomy (2), with lymph node resection (1): papillary carcinoma, thyroid
Lymphoepithelioma	No biopsy: treatment initiated (1)
Leukemia	
Acute myelocytic	No biopsy: treatment initiated (1)
Acute lymphocytic	No biopsy: treatment initiated (3)
Lymphoma	
Hodgkin's disease	Biopsy: Hodgkin's disease (1)
Large-cell lymphoma	Biopsy: true histiocytic lymphoma (1)
Sarcoma	
Rhabdomyosarcoma (embryonal or alveolar)	Biopsy: embryonal rhabdomyosarcoma (1); no biopsy: treatment initiated (2)
Undifferentiated sarcoma	No biopsy: treatment initiated (1)
Malignant schwannoma	Stump revision: traumatic neuroma (1)
Malignant histiocytosis	No biopsy; treatment initiated (1)
Eosinophilic granuloma	Thyroidectomy: eosinophilic granuloma (2); no biopsy of involved lymph node (1)

cm in greatest dimension and contained an area of central sclerosis. On microscopic examination, a papillary thyroid carcinoma was noted that contained both microfollicular and papillary patterns. Capsular and vascular invasion was noted. Metastatic tumor was seen in the excised left posterior cervical lymph node (Figure 1-B) and in tissue from the anterior trachea. The patient was treated postoperatively with chemical thyroid ablation and is well a year later.

Case 2

The patient, a 7-year-old girl in acute respiratory distress, was noted to have cervical lymphadenopathy and hepatosplenomegaly on physical examination. She was found to have an enlarged right supraclavicular node on which FNAB was done. Smears and cytospin preparation revealed abundant atypical lymphoid cells characterized by enlarged, eccentrically placed nuclei with anisonucleosis and one or more macronucleoli. Most cells had abundant amphophilic cytoplasm (Figure 2-A). Large-cell lymphoma was diagnosed. Immunoperoxidase stains for lymphoid markers—including T11, Leu14, B1, B4, My7, and κ and λ light chains—were performed on cytospin preparations of the aspirated material. Between 70% and 80% of the large cells stained positively with My7, suggesting a lymphoma of true histiocytic origin.

The aspirated lymph node was removed, and a diagnosis of true histiocytic lymphoma was confirmed by immunoperoxidase staining positive for MT-1, LN-2, and α_1-antichymotrypsin (Figure 2-B). No staining was noted for light chains or LN-1.

Malignant cells were noted subsequently in specimens of bronchial washings, pleural fluid, and skin. The patient died of infectious complications two months after the diagnosis was made.

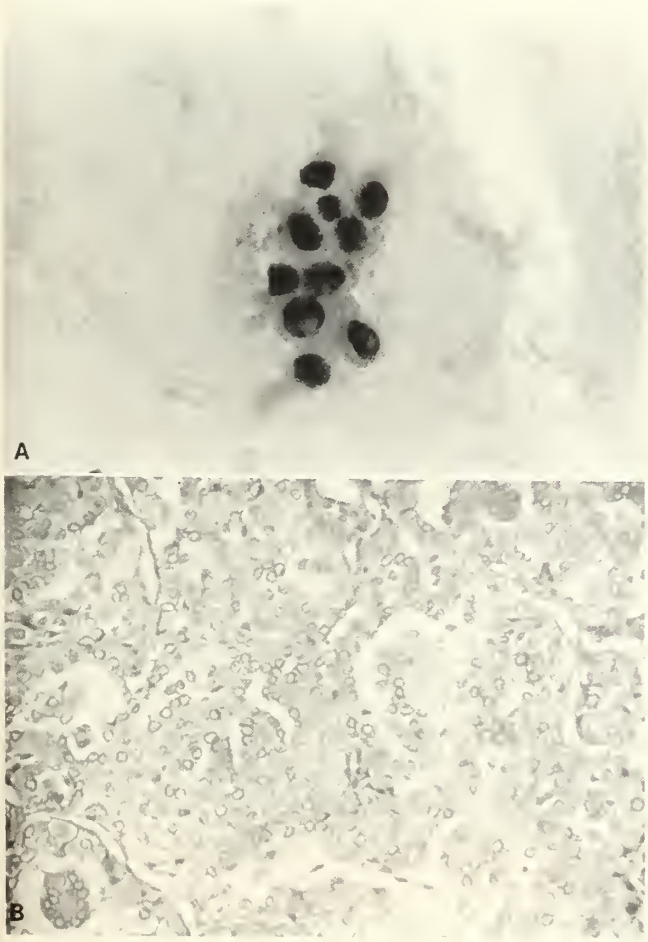

Figure 1.—**A,** The intranuclear vacuole and grooves are characteristic of papillary carcinoma of thyroid (Papanicolaou stain, original magnification × 400). **B,** A cervical lymph node shows metastatic papillary carcinoma of thyroid (Papanicolaou stain, original magnification × 250).

Case 3

The patient, a 3-year-old girl with a history of a below-the-knee amputation for malignant schwannoma two years previously, was noted by her grandmother to have a 1-cm, soft nodule at the distal end of her amputation stump. On FNAB, the nodule felt soft to the aspirating needle, and yellow, mucoid material was obtained. Smears revealed abundant spindle-shaped cells arranged singly and in groups with plump nuclei, some anisonucleosis, and small but conspicuous nucleoli (Figure 3-A). The cytologic material appeared similar to the patient's original tumor (Figure 3-B). Immunoperoxidase staining of the aspirated material was positive only for vimentin. Although this finding was similar to the original tumor, benign connective tissue in that site would stain similarly, and the immunoperoxidase results were therefore considered noncontributory. On the basis of the abundant cellularity, slight atypia, and similarity to the original tumor, recurrent malignant schwannoma was diagnosed. The patient's stump was revised to an above-the-knee amputation. Extensive dissection of the surgical specimen revealed a large traumatic neuroma composed of numerous small, reactive neural bundles within a loose, myx-

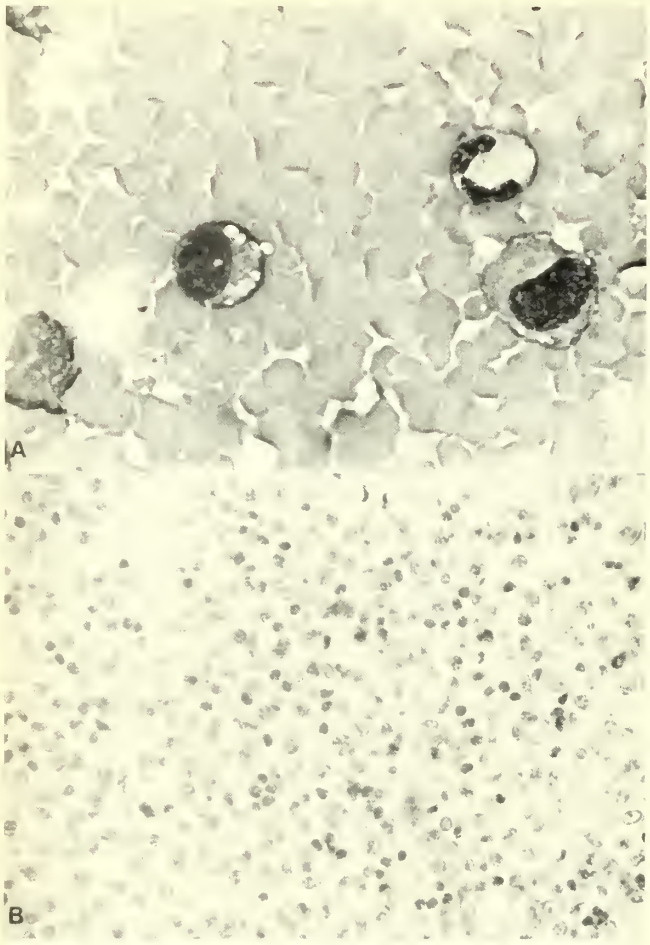

Figure 2.—**A,** The dyshesive lymphoma cells have enlarged, eccentric nuclei (Wright-Giemsa stain, original magnification × 1,000). **B,** A lymph node shows true histiocytic lymphoma (hematoxylin and eosin stain, original magnification × 250).

oid, fibrous stroma (Figure 3-C). There was no evidence of sarcoma.

Discussion

In adults, the use of FNAB has become popular for evaluating superficial and deep masses. The procedure is considered the standard of care in the diagnosis of masses in the breast, thyroid, head and neck, and other sites. Its accuracy ranges from 80% to 97%.[8(p6)] American physicians have been reluctant to adopt its use for children, however, even though it is generally accepted that an atypical course of what otherwise appears to be a common childhood condition—especially a persistent, unexplained, or growing mass—should receive prompt evaluation.[9]

There are probably many reasons why FNAB has been underused in the initial evaluation of these masses. Many physicians believe that a highly suspicious mass may require surgical excision despite FNAB and that therefore FNAB is redundant and unwarranted. As shown by this study, FNAB was able to obviate surgical intervention, allowing treatment to be initiated immediately in many patients. Even in those in whom an operation was still required, preoperative FNAB helped eliminate anxiety before and during the operation because the clinician could inform the patient and family of the probable diagnosis before the operation and discuss treatment options fully. The surgeon could thus plan a definitive surgical approach and avoid a frozen section or a two-stage procedure with excisional biopsy followed by resection.

Clinicians may be reluctant to use FNAB in cases in which the clinical suspicion of malignancy is low, fearing that the procedure is too traumatic, and usually prefer to observe the patient clinically. A persistent mass is still worrisome, however, and the diagnosis of cancer is often delayed because

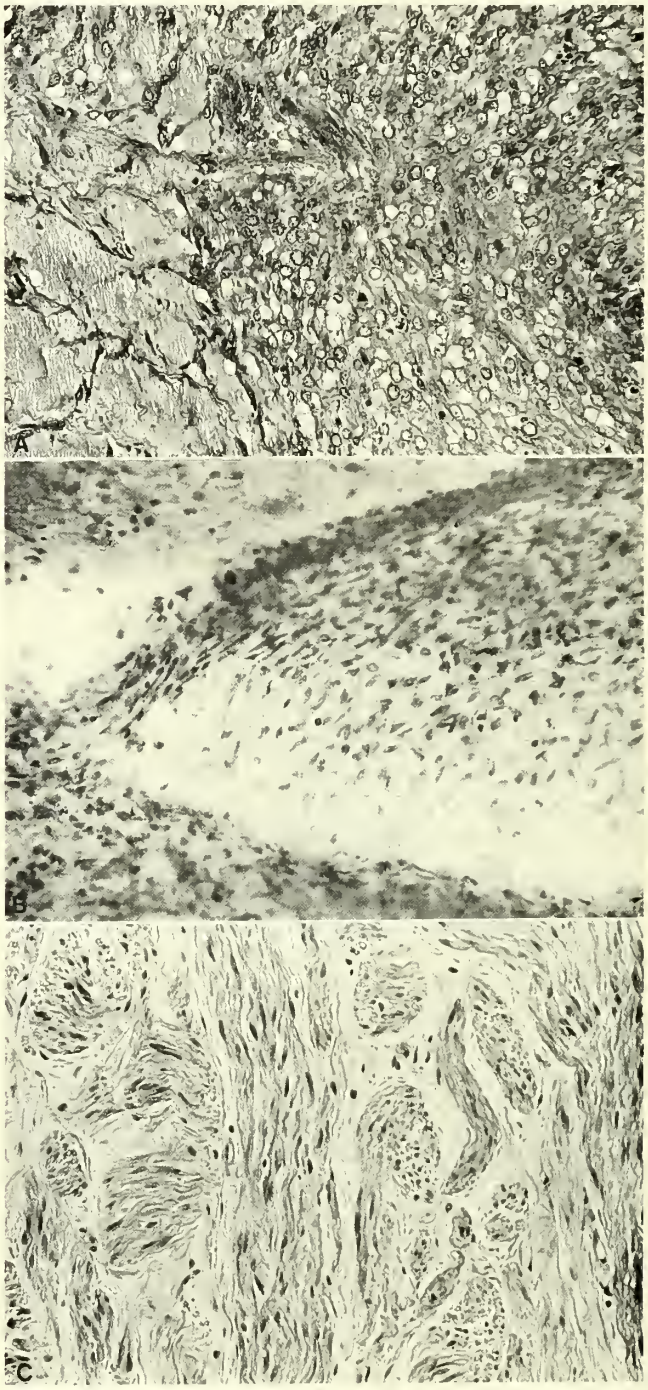

Figure 3.—**A,** Highly cellular aspirate contains abundant spindle cells with plump nuclei thought to represent recurrent malignant schwannoma (Wright-Giemsa stain, original magnification × 250). **B,** A cytologic specimen shows malignant schwannoma of the right leg. Note the cellular spindle cell configuration with plump nuclei but minimal nuclear pleomorphism (hematoxylin and eosin stain, original magnification × 250). **C,** A specimen of traumatic neuroma from an amputation stump of the right leg shows loose mucoid material surrounding some proliferating nerve fibers (hematoxylin and eosin stain, original magnification × 250).

of the clinical assumption of an infectious or reactive process. Fine needle aspiration biopsy gives the patient, parents, and clinicians reassurance that the lesion has been sampled and, if deemed benign, that clinical follow-up is not blind.

In our experience, FNAB of superficial masses in children is no more painful or traumatic than drawing blood or doing a spinal tap, both of which are common in the workup of an acutely ill child. Sedation is usually not required. To avoid upsetting a child before a specimen is obtained, we typically do not give local anesthetic, although older children may be given that option. The needle and syringe are kept out of the patient's sight because some children find them frightening. With a parent or assistant immobilizing the child, a 22- or 25-gauge needle is inserted into the mass. Usually two, and often three, aspirations are performed easily. We typically do a rapid stain, either with a modified Wright-Giemsa stain or toluidine blue, and evaluate the material from the first aspirate immediately to ascertain that the needle is within the mass, to determine whether an adequate specimen has been obtained, and to gain an impression of the type of lesion present. This greatly assists in the assessment of material from subsequent passes. Material from additional passes can then either be used to make more smears, be injected into a supportive medium (such as RPMI) from which multiple cytospins can be prepared for various staining purposes, or be prepared for culture. The procedure is safe, and there are almost no contraindications. A small bruise at the aspiration site is the most common complication. Tumor spread along the needle tract or infectious complications are extremely rare, and extensive use of FNAB in adults has shown these problems to be almost nonexistent.[10-12]

A common misconception is that FNAB does not collect an adequate quantity of material for accurate diagnosis. As shown by cases 1 and 2, a complete workup, including immunoperoxidase staining, can be done on aspirated material from both solid and hematologic malignant lesions. Electron-microscopic examination of cytologic material is also possible and has proved useful in the diagnosis of tumors in children.[13-17] In our series, FNAB was sufficiently accurate to increase clinical understanding and provide a guide to therapy in 40 of 50 cases in which adequate material was obtained and made surgical biopsy unnecessary in 32 of those cases. A 3% false-positive and false-negative rate in children has been reported.[2-4] Other studies have shown a positive predictive value of 95% and sensitivity and specificity of 97%.[6] It is important to note that in none of our 54 cases did FNAB delay or interfere with a patient's subsequent workup.

Because most malignant neoplasms in children are lymphomas, and because the classification of lymphomas is based on both cell detail and histologic architecture, physicians may have the misconception that FNAB is not useful in the evaluation of children with persistent lymphadenopathy. The procedure can, however, play an important role in preparing these patients for excisional biopsy. In the primary diagnosis of lymphoma, as in case 2, excisional biopsy may still be necessary to subclassify the lesion fully. As the other lymph node aspirates in this series show, however, patients with a cytologic diagnosis of benign lymphoid hyperplasia or with a specific benign diagnosis, such as cat-scratch disease, can be observed clinically and need not undergo an operation. We also found FNAB to be useful in following up patients with a history of cancer to evaluate recurrence, progression, infectious complications, or, as in case 1, the development of an unsuspected second primary tumor. In a recent study of lymph node FNAB in young patients, a sensitivity and specificity of 93% and 95%, respectively, were reported.[4]

Although FNAB can be accurate, not all cases are straightforward, and case 3 illustrates a diagnostic problem. A false-positive diagnosis is a dreaded result for the pathologist, clinician, and patient. Spindle cell lesions are particularly difficult because benign lesions can mimic sarcoma both cytologically and histologically; therefore, diagnosis in this area should be made with caution. The reactive proliferating nerve fibers and fibroblasts of the traumatic neuroma in case 3 appeared similar to the patient's original tumor; in retrospect, however, careful microscopy shows that the original tumor cells are larger and have plumper nuclei than those in the aspirate. Reactive fibroblasts have been the cause of a previously reported false-positive FNAB diagnosis in a child with a history of sarcoma.[6] Fortunately, false-positive aspirates are rare, and the technique's accuracy in adults has contributed to its popularity.[8] Even the "gold standard" of tissue histopathologic features is not 100% accurate. Perhaps the clinical context should have been more of a clue to the benign nature of the lesion. The clinician did not particularly suspect recurrence; whenever the clinical and cytologic impressions do not coincide, a tentative diagnosis rather than one definitive for malignancy may be preferable. Close cooperation between clinician and pathologist is essential for accurate interpretation.

Potential difficulty in interpreting FNAB in children emphasizes the importance of having an experienced cytopathologist available for an accurate diagnosis. Errors in diagnosis usually are caused by lack of experience.[18] Most dedicated pediatric hospitals do not have pathologists specifically trained in this subspecialty, and most cytopathologists practice in adult hospitals and have little experience with the cytologic appearance of pediatric masses. These deficiencies have probably contributed greatly to the underuse of this technique in children. Although clinicians do not employ FNAB for diagnostic purposes if experienced interpreters are not available, pathologists cannot gain the necessary experience without opportunities to examine cytologic material from children, thus creating a vicious circle. A staged program to implement FNAB has been recommended and proved successful.[19]

Because cancer causes more deaths in children than any other disease in the United States,[20] and because malignant tumors can mimic common, benign childhood conditions, persistent and growing masses should be subjected to FNAB as part of the initial diagnostic workup. Physicians caring for children should use this technique because of its safety, accuracy, and ease of use and should encourage the development of interpretive expertise among their pathologist colleagues.

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ON AN OLD WOMAN DYING

Something was marred in making at her birth.
Neither the mind nor body prospered well.
In a short time the flesh was old and ill.
The child's intelligence, a childish mirth,
Halted its growth to live in that sad frame,
Life difficult and strange, and none to blame.

Unjust detention! Loneliness and pain
And ridicule pursued her all her days.
Yet in her speech and fierce bewildered gaze
The shyest child might read affection plain.
Daily she begged us to accept her love,
In charity to accept her and approve.

Now she is dying, and, half-blind with age,
The eyes peer dimly; now love may discern
Momently in their shades the gay return
Of courage, dissolution to assuage.
Let it be this in naming her we name.
This at her death may lasting radiance claim.

JANET LEWIS©
Los Altos, California

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Nonsteroidal Anti-inflammatory Drugs
Proposed Guidelines for Monitoring Toxicity

THOMAS M. BUSH, MD; TAMMI L. SHLOTZHAUER, MD; *and* KENT IMAI, MD, *San Jose, California*

The most common toxicities of nonsteroidal anti-inflammatory drugs (NSAIDs) are gastropathy, renal dysfunction, and liver function abnormalities. We outline an approach to monitoring patients on long-term NSAID therapy, focusing on the early detection of complications.

Gastropathy caused by NSAID use is more common in elderly patients or those with a history of dyspepsia, peptic ulcer disease, or alcohol abuse. Fecal occult blood testing and hemograms are less accurate in detecting gastropathy than direct visualization but are convenient and relatively inexpensive. We recommend the periodic use of these tests to detect NSAID-induced acute or chronic blood loss. Renal toxicity is seen in patients with preexisting renal disease or functional volume depletion and in the elderly. Complications include renal insufficiency, hyponatremia, hyperkalemia, and proteinuria. Renal function should be monitored during the first few weeks of NSAID therapy, especially in high-risk patients, with periodic testing thereafter. Hepatic toxicity is less common but warrants occasional determinations of alanine aminotransferase levels. Elderly patients and those with renal insufficiency or alcohol abuse have a higher risk of complications.

Nonsteroidal anti-inflammatory drugs should be used cautiously in those patients at high risk for complications. Strategies can be used to limit toxicity. Patients taking these drugs long term should be monitored periodically for signs of blood loss, renal dysfunction, and hepatic dysfunction.

(Bush TM, Shlotzhauer TL, Imai K: Nonsteroidal anti-inflammatory drugs—Proposed guidelines for monitoring toxicity. West J Med 1991 Jul; 155:39-42)

Nonsteroidal anti-inflammatory drugs (NSAIDs) are taken by approximately 10% of patients.[1] Though generally well tolerated, various toxic effects can occur. Rashes and central nervous system toxicity are generally mild reactions detected easily by history and physical examination.[2,3] Pulmonary and idiosyncratic hematologic toxicities are largely unpredictable but fortunately rare.[3] Gastropathy, renal dysfunction, and liver function abnormalities are relatively common and often symptomatic only after serious toxic reactions have occurred.[4-6] We will review the incidence of these three common NSAID toxicities and propose an approach to appropriate monitoring.

Gastropathy

Incidence

Upper gastrointestinal (GI) tract bleeding is the most common serious complication of NSAID use. Barrier and Hirschowitz have reviewed endoscopic studies that uniformly show a high rate of gastric erosions and ulcers in patients taking NSAIDs.[4] Nearly a third (30%) of patients have dyspepsia. Endoscopy of these patients shows 20% with normal mucosa, 50% with erosions and petechiae, and 30% with gastric ulcers. In 70% of patients, dyspepsia does not develop. In these patients, the findings on endoscopy are a normal mucosa in 50%, erosions and petechiae in 45%, and gastric ulcers in 5%. Therefore, gastric ulcers will develop in about 12.5% of patients on NSAID therapy, a third of whom are asymptomatic.

Despite the high rate of gastric lesions seen on endoscopy, the rate of clinical bleeding in patients taking NSAIDs in a large retrospective study by Carson and co-workers was relatively low: 1.5 substantial upper GI bleeding episodes per 1,000 patient-years on NSAID therapy versus 1 per 1,000 patient-years without NSAID use.[1] This reflects a low risk for the average patient using NSAIDs. The rate of upper GI tract bleeding in patients with multiple risk factors is probably considerably higher.

Risk Factors

Well-established risk factors for serious upper GI bleeding on NSAID therapy include being older than 60 years,[1] a history of peptic ulcer disease, dyspepsia with NSAID use,[4] cigarette[7] and alcohol use, high-dose and prolonged NSAID use,[1] and serious concomitant disease. Graham and Smith did not find low-dose aspirin prophylaxis to be associated with a higher risk of upper GI bleeding.[8]

Monitoring

The diagnostic tests that could detect clinically significant NSAID-induced gastropathy include fecal occult blood testing, hemograms, upper GI tract roentgenograms, and upper GI endoscopy.

Fecal occult blood testing is less sensitive for upper GI tract blood loss than for lower GI tract blood loss. Ostrow and colleagues have shown that 25 ml of gastric blood loss is required for Hemoccult detection, whereas Hemoccult screening detects 5 ml per day of colonic blood loss.[9] Patients using NSAIDs who have a positive Hemoccult test were found by Bahrt and associates to have more colonic neoplasms than upper GI ulcers.[10]

From the Department of Medicine, Divisions of Rheumatology (Drs Bush and Shlotzhauer) and Primary Care (Drs Bush and Imai), Santa Clara Valley Medical Center, San Jose, California.

Reprint requests to Thomas M. Bush, MD, Santa Clara Valley Medical Center, 750 S Bascom Ave, San Jose, CA 95128.

ABBREVIATIONS USED IN TEXT

ALT = alanine aminotransferase
GI = gastrointestinal
NSAIDs = nonsteroidal anti-inflammatory drugs

Hemograms may be useful in detecting a microcytic anemia, which generally develops when blood loss exceeds 20 to 30 ml per day.[4] There has been little evidence, however, to suggest that hemograms are adequately sensitive to alert clinicians to the presence of a severe gastropathy or an impending massive upper GI hemorrhage. Doube and Collins have shown a poor correlation between hemogram results and endoscopically demonstrated gastropathy.[11]

Visualization of the upper GI tract by endoscopy is highly sensitive and specific but too expensive for routine screening. Upper GI roentgenograms are probably less useful. These studies should be reserved for patients who are still symptomatic with dyspepsia after medical therapy has been modified or for those who have evidence of blood loss.

Clinical studies have not adequately clarified the usefulness of fecal occult blood tests and hemograms in detecting early blood loss from gastropathy. Hemograms can accurately detect chronic blood loss resulting from prolonged NSAID use. Fecal occult blood tests may indicate recent heavy upper GI bleeding. Although these tests are much less accurate than direct visualization of the upper GI tract, they are noninvasive and relatively inexpensive. A positive fecal occult blood test or abnormal hemogram results should lead to a change in the patient's management (see Alternative Therapy section), even though the site of bleeding may not be immediately apparent. We recommend that patients on ongoing NSAID therapy be monitored periodically for signs of blood loss. In addition, all patients should be instructed to promptly report dyspepsia or melena.

Monitoring Guidelines for Detecting NSAID Gastropathy

- Asymptomatic or low-risk patients: An initial hemogram and fecal occult blood test should be done within the first 3 months and repeated every 6 to 12 months.
- Symptomatic or high-risk patients: An initial hemogram and fecal occult blood test should be done within the first month and repeated every 3 to 6 months; consider alternative therapies.

A notable decrease in the hemoglobin level or mean erythrocyte volume or a positive fecal occult blood test should lead to the discontinuation of NSAIDs. If a patient also complains of dyspepsia or melena, a prompt evaluation of the upper GI tract is warranted. In asymptomatic patients, the hemogram should be repeated. If there is no sign of continued blood loss, the clinician may consider the cautious use of NSAIDs that have less upper GI toxicity along with an agent to protect the gastric mucosa (see Alternative Therapy). Persistent anemia or occult bleeding may indicate an upper GI tract disorder or a malignant neoplasm of the colon in patients at risk and should be evaluated accordingly.

Renal Toxicity

Incidence

Renal toxicity due to NSAID therapy is uncommon in healthy persons, but the incidence can approach 20% in patients at high risk.[5] The most common toxic effect is hemodynamically mediated renal insufficiency due to the inhibition of renal prostaglandin synthesis.[12] A recent prospective clinical trial by Whelton and co-workers has shown that in patients with renal insufficiency, an abrupt increase in creatinine levels can occur within seven to ten days of the initiation of a regimen of a short-acting NSAID.[13] Gurwitz and associates found reversible azotemia in 13% of elderly patients treated with NSAIDs.[14]

TABLE 1.—*Risk Factors for Acute Renal Failure with Nonsteroidal Anti-inflammatory Drug Therapy*

Age older than 60
Atherosclerotic disease
Diabetes mellitus
Extracellular volume depletion
Hemorrhage
Diuretics
Extrarenal salt loss
Decreased effective volume
Congestive heart failure
Cirrhosis
Nephrotic syndrome
Other high renin-angiotensin states
Anesthesia
Renal artery stenosis
Sepsis
Preexisting renal parenchymal disease

The use of NSAIDs can induce hyperkalemia, which occasionally may be life threatening.[15] These drugs can also affect sodium and water balance, with sodium retention leading to edema or water retention causing hyponatremia.[12] All these effects are predictable in high-risk patients and reversible with the cessation of the drug.[14] Parenchymal diseases due to NSAID use, including the nephrotic syndrome, interstitial nephritis, and papillary necrosis, are largely unpredictable but fortunately rare. Nonsteroidal anti-inflammatory drugs can also interfere with the antihypertensive effect of diuretics and β-blockers.[12]

Risk Factors

The risk factors for acute renal insufficiency include age older than 60, vascular disease,[5] real or functional volume depletion,[14] preexisting renal insufficiency, high renin-angiotensin states, and systemic lupus erythematosus[12] (Table 1). Patients at high risk for hyperkalemia developing include elderly persons, those with preexisting renal disease, and patients taking potassium-sparing diuretics, potassium supplements, angiotensin-converting enzyme inhibitors, and β-blockers.[15] Patients at risk for hyponatremia developing are those taking thiazide diuretics.[12]

Monitoring

It has been shown that NSAIDs can interfere with renal function within the first few weeks of therapy. This effect is seen predominantly in patients with preexisting renal disease. Therefore, an initial assessment of renal function is necessary to determine a patient's risk of NSAID toxicity. Interstitial nephritis and nephrotic syndrome can occur sporadically, and a patient's hemodynamic status will vary with time. Thus, it seems appropriate to periodically monitor the renal function of patients on long-term NSAID therapy.

Monitoring Guidelines for Detecting NSAID-induced Renal Toxicity

To monitor patients for renal insufficiency, hyperkale-

mia, hyponatremia, and proteinuria due to NSAID use, we propose the following guidelines:

- Low-risk patients: Measure serum sodium, potassium, blood urea nitrogen, and creatinine levels and do a urinalysis within 3 months; repeat these studies every 6 to 12 months.
- High-risk patients: Measure serum sodium, potassium, blood urea nitrogen, and creatinine levels and do a urinalysis within 1 to 3 weeks; repeat these studies every 3 to 6 months; consider alternative therapies.

Elevated blood urea nitrogen, creatinine, or potassium levels, the appearance of proteinuria, or a decrease in the sodium concentration should lead to the discontinuation of NSAIDs. Patients should undergo a prompt clinical evaluation to screen for other causes of renal deterioration. A cautious reintroduction of NSAIDs with less renal toxicity may be attempted after a patient's renal function returns to baseline.

Hepatic Toxicity

Incidence

Paulus reported on a prospective trial of 7,000 patients taking NSAIDs.[6] Of these, 3% had persistent abnormalities (elevations) on more than one liver function test. Clinical hepatitis, cholestasis, and hepatic necrosis are rare. Abnormalities in liver function are almost always reversible with the cessation of NSAIDs.[16]

The mechanism of hepatic injury is varied. Salicylates appear to be predictable, dose-related hepatotoxins; other NSAIDs have idiosyncratic hepatic effects that may be due to hypersensitivity responses or metabolic changes. Hypersensitivity responses generally occur within the first four to six weeks. Other toxic hepatic reactions usually occur within three months.[16]

Risk Factors

Established risk factors are advanced age, renal insufficiency, multiple drug use,[6] alcohol use,[17] and higher drug doses[16] (Table 2).

Monitoring Tests

The consensus of the Food and Drug Administration's Arthritis Advisory Committee was that elevated aspartate or alanine aminotransferase (ALT) levels were an early warning of reversible liver toxicity.[6] The committee was concerned that continued NSAID use could result in more severe liver damage. Significant morbidity from NSAID-induced liver toxicity is uncommon in low-risk patients. If a prolonged course of NSAIDs is anticipated, we recommend an early evaluation of hepatic function. Periodic monitoring appears prudent in long-term NSAID users.

Monitoring Guidelines to Detect NSAID-induced Liver Toxicity

- Low risk: Initial ALT (SGPT) levels should be monitored within the first three months of therapy; repeat every 6 to 12 months.
- High risk: Initial ALT levels should be monitored within the first month of therapy; repeat every 3 to 6 months; consider alternative therapy.

A threefold elevation of the ALT level should lead to the discontinuation of NSAIDs. If the ALT level does not return to baseline, further investigation for hepatic disease is required. If the ALT level returns to normal, alternative NSAIDs could be cautiously instituted. A patient with a mild baseline ALT elevation should be monitored according to the guidelines for high-risk patients.

TABLE 2.—*Risk Factors for NSAID Hepototoxicity*

Age older than 60
Renal insufficiency
Multiple drug use
High NSAID dosage
Prolonged NSAID therapy
Alcohol use
Systemic lupus erythematosus
Juvenile arthritis

NSAID = nonsteroidal anti-inflammatory drug

Alternative Therapy

If a patient has been determined to be at high risk for NSAID-induced gastropathy, renal toxicity, or hepatitis, various alternative therapeutic maneuvers should be considered. These include a lower dose NSAID regimen, non-NSAID analgesics, topical balms, and the use of other methods of pain relief such as physical therapy, acupuncture, and biofeedback.

For those patients who are at high risk for gastropathy, the use of NSAIDs with a lower gastrointestinal toxicity profile such as salsalate or magnesium choline trisalicylate should be considered.[18,19] Ulcers caused by NSAID use tend to be gastric and non-acid-dependent and, thus, less responsive to histamine$_2$ blockers and antacids.[20] Misoprostol, a prostaglandin analogue, has recently been shown to be effective in preventing NSAID ulcers.[21] Edelson and associates have shown that misoprostol is cost effective for prophylaxis against NSAID-induced upper gastrointestinal bleeding in high-risk patients.[22] Sucralfate has also been found in some studies to protect the gastric mucosa.[20] Omeprazole, a new proton pump inhibitor, was shown in a small clinical study by Daneshmend and colleagues to prevent aspirin-induced gastric mucosal injury.[23] Clinicians may consider the use of one of these agents in high-risk patients who require ongoing NSAID therapy.

Patients at risk for renal toxicity should also be considered for the use of salsalate or magnesium choline trisalicylate. These agents in moderate doses have less inhibition of prostaglandin synthesis and a generally safer renal profile.[19]

Summary

There are no controlled, prospective trials on the usefulness of monitoring for the early detection of NSAID-induced gastric, renal, or hepatic toxicity. We have reviewed the incidence of these complications, identified risk factors, and suggested guidelines for NSAID monitoring. All patients should be instructed in the common side effects of NSAIDs and encouraged to report any relevant symptoms. It is important to determine which patients are at high risk for NSAID toxicity. These patients should be monitored more carefully than low-risk patients, and, whenever possible, alternative therapies should be considered.

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This article is one of a series on topics in primary care in which common diagnostic or therapeutic problems encountered in primary care practice are presented. Physicians interested in contributing to the series are encouraged to contact the Special Editors.

STEPHEN M. McPHEE, MD
TERRIE MENDELSON, MD
Special Editors

Articles

Is Deleting the Digital Rectal Examination a Good Idea?

MARK A. SUTTON; ROBERT P. GIBBONS, MD; *and* ROY J. CORREA, Jr, MD, *Seattle, Washington*

Many groups have taken the position that the digital rectal examination should be discontinued as part of the annual screening physical examination. We examined the effects of not doing a digital rectal examination on the early diagnosis of prostate cancer. The average time since a previous rectal examination increased as the stage of cancer increased. The digital rectal examination proved to be a relatively insensitive test, with 40% of stage D cancers being detected initially within 12 months of the most recent examination. Nevertheless, an annual digital rectal examination did detect a greater percentage of lower stage (and thus more localized and potentially curable) cancers when repeated within 12 months. When the last rectal examination was more than 24 months previous, cancers detected were more likely to be advanced.

Without a digital rectal examination, patients would have their disease detected only by the presence of symptoms. When it was done because of symptoms, 81% of our patients had stage D cancers compared with 32% of stage B and 38% of stage C patients. Without the routine use of this examination, patients with prostate cancer would be more likely to have higher stage and less potentially curable lesions at the time of diagnosis. We conclude that the digital rectal examination remains an important part of routine annual physical examinations.

(Sutton MA, Gibbons RP, Correa RJ Jr: Is deleting the digital rectal examination a good idea? West J Med 1991 Jul; 155:43-46)

Carcinoma of the prostate is a disease rarely seen in men younger than 45 years of age. After that age, however, the incidence of the disease increases until possibly half or more of the male population over the age of 70 is affected.[1] Numerous autopsy studies of men over age 40 who have died of various causes reveal that more than 30% have unsuspected prostate cancer.[2,3] One autopsy report found 10% of men between the ages of 50 and 59 to have this cancer, with the incidence rising to 40% to 50% in men older than 70 years.[4] Therefore, prostate cancer is a prevalent histologic finding at autopsy.

Despite this high incidence, most of these cancers have proved to be of no clinical significance. In one autopsy series, this subclinical rate of disease was 95%.[4] In fact, for every patient who dies of prostate cancer, 380 remain asymptomatic and have unsuspected histologic cancer detected at autopsy.[5] With the aging male population, however, clinical disease is being detected in an increasing number of patients. It is estimated that this year in the United States, more than 106,000 new cases of adenocarcinoma of the prostate will be diagnosed and more than 30,000 deaths will occur.[6] In 1990, prostate cancer was the second most common cause of death from cancer for men.[6]

Definitive therapeutic approaches to treat prostate cancer currently include surgical and radiation therapy. These have been shown to be most effective in patients with low-stage (localized) cancers.[7,8] Therefore, if carcinoma of the prostate is detected and definitive treatment is begun early, fewer deaths should occur.

Unfortunately, tests to detect early prostate cancer are limited, with only three currently available. One is transrectal ultrasonography, but this imaging study is new and is still undergoing performance testing for sensitivity and specificity. Early evidence suggests a positive predictive value of 31%, with the large number of false-positive tests caused by similar sonographic appearance between prostatic carcinoma and benign conditions such as prostatitis and prostatic infarction.[9] The second test is for serum tumor markers such as prostatic acid phosphatase and prostate-specific antigen. Prostatic acid phosphatase measurements have moderate sensitivity (20% to 45%) while the prostrate-specific antigen test is highly sensitive but lacks specificity (38% to 56%).[10-12] Therefore, transrectal ultrasonography and the tests for serum tumor markers have not been endorsed by the scientific medical community as efficient, dependable, and cost-effective screening tests for prostate cancer.

The third test is the oldest: digital rectal examination (DRE). Championed in the early 1900s by Young[13] and later by Kimbrough,[14] this physical examination has recently come under discussion as a reliable early detection technique. The sensitivity of DRE is limited because the cancer may not have a different "feel" from the surrounding benign tissue or may be beyond the reach of the examining finger.[15-17] One study of asymptomatic men found the sensitivity of DRE to be only 33%.[18] Others place the sensitivity as low as 2% to 9%.[19] The DRE also has limited specificity, producing a large proportion of false-positive results. Several studies of asymptomatic men found that only 26% to 34% of men with a suspicious finding on DRE actually had histologic evidence of cancer on needle biopsy.[5,9,20] Other studies of men with urinary obstructive symptoms reveal that when the DRE is combined with other diagnostic tests, it has a sensitivity of 69% to 73% and a specificity of 77% to 89%.[10,21] Because of the patient population used in these studies, however, the results probably cannot be generalized to asymptomatic men. In addition, the exact sensitivity and specificity of the DRE are unknown because biopsies are rarely done on men with normal DRE results.

With these facts in mind, groups around the world have begun investigating the necessity of doing the DRE as a rou-

From the University of Washington School of Medicine (Mr Sutton) and the Section of Urology and Renal Transplantation, Virginia Mason Clinic (Drs Gibbons and Correa), Seattle, Washington.

Reprint requests to Robert P Gibbons, MD, Virginia Mason Clinic, C7-UR, 1100 Ninth Ave, PO Box 900, Seattle, WA 98111.

tine part of the general physical examination. As these groups assembled the "adult preventive medicine examination," tests that had not been proved on the basis of a rigorous classification system were not recommended for continuation as screening tests. As a result, the DRE was not recommended for use in the annual physical examination by the Canadian Task Force[22] or by other experts.[23,24] Because of these conflicting positions, this study was done to address the following questions: How would the removal of the DRE from the routine physical examination affect the diagnosis of prostate cancers in the general population? Are serial DREs effective in detecting prostate cancer at an earlier and more successfully treatable stage?

Patients and Methodology

A retrospective, case review format was used in which 103 patients with stage B (tumor confined to the prostate), 55 patients with stage C (local spread of tumor into adjacent structures), and 52 patients with stage D (distant metastatic disease) prostate cancer were selected from the Virginia Mason Hospital (Seattle, Washington) tumor registry files. A total of 310 medical records were reviewed for information on six individual points: the patient's age at diagnosis, how the diagnosis was considered, how the diagnosis was established, the date of the last previous DRE, who did the previous DRE, and whether the same examiner did the DRE that was diagnostic for cancer (Figure 1). Any record that did not contain exact information on the above-stated points was eliminated. Only initial cancers were considered, and the records of patients with recurrent cancer were eliminated from consideration. Stage A patients were excluded because these cancers are by definition microscopic and not detectable by DRE.

Results

Stage B patients had an average age at diagnosis of 64.0 years, stage C patients averaged 70.1 years, and stage D patients averaged 74.7 years of age (Table 1). Carcinoma of the prostate was considered by either an abnormal DRE or by symptoms such as back pain, obstructive symptoms, dysuria, frequency, nocturia, urgency, hematuria, and incontinence. Approximately two thirds of the stage B and C patients (68% and 62%, respectively) were considered by abnormal DRE findings and had no symptoms, whereas 81% of the stage D patients presented with symptoms. If the diagnosis was not considered until symptoms developed, there was a significant probability that a patient had metastatic versus confined disease ($P < .01$).

All patients had their prostate cancer confirmed by needle biopsy.

The time since the previous DRE was done was divided into the percentage of cancers that occurred within the past 12 months, between 12 and 24 months, and more than 24 months (Table 2). More than half (52%) of the stage B, 65% of the stage C, and 40% of the stage D patients had their prostate cancer diagnosed within 12 months of the most recent previous DRE. On the other hand, 23% of the stage B, 25% of the stage C, and 40% of the stage D patients had their prostate cancer diagnosed after an interval of more than two years since the last DRE. If palpable evidence of prostate cancer developed more than two years after a patient's last rectal examination, there was a significant probability that he had metastatic versus confined disease ($P < .05$).

The average time since the last previous DRE was done was 21.1 months for stage B, 26.9 months for stage C, and 49.7 months for stage D patients (Table 2). Again, there was a demonstrated advantage to detecting localized stage B or C disease with more frequently performed DREs ($P < .056$).

The examiners who did the last previous DRE fell into three specific groups: urologists; primary care physicians, consisting of family physicians, general practitioners, general internists, and internal medicine subspecialists; and all others, such as surgeons and nurses. Approximately a third of the previous DREs were done by urologists (35.0%, 34.5%, and 36.5% for stages B, C, and D, respectively), with the remaining two thirds done by primary care physicians (62.1%, 61.8%, and 63.5% for stages B, C, and D, respectively). Previous DREs done by persons other than urologists and primary care physicians were rare (2.9%, 3.6%, and 0%

TABLE 1.—*Patient Populatian and How the Original Diagnosis Was Considered*

Cancer Stage	No.	Age, yr Average (Range)	Diagnosis Considered by Rectal Exam, %	Symptoms,* %
B	103	64.0 (45 to 77)	68	32
C	55	70.1 (58 to 80)	62	38
D	52	74.7 (61 to 93)	19	81

*Stage D versus stages B and C, $P < .01$.

Patient Name					
Clinic Number					
Date of Birth					
Date of Diagnosis					
Stage at Diagnosis					
? Diagnosis Considered					
? Diagnosis Established					
Date of Previous Rectal Exam					
Previous Rectal Done By?					
Same Rectal Examiner?					
Date of Treatment					
Type of Treatment					
Date of Recurrence					
Type of Recurrence					
Date of Death					
Cause of Death					

Figure 1.—The form shows the information collected on each patient from hospital records.

TABLE 2.—*Time Since the Last Previous Digital Rectal Examinatian (DRE) Was Done*

Cancer Stage	No.	Patients Receiving DRE in < 12 mo, %	12 mo to 24 mo, %	> 24 mo,* %	Average Time Since Last DRE, mo
B	103	52	25	23	21.1
C	55	65	9	25	26.9
D	52	40	19	40	49.7†

*Stage D versus stages B and C, $P < .05$
†Stages B and C versus D, $P = .056$.

TABLE 3.—*Time Since Urologist Did Last Previous Digital Rectal Examination (DRE)*

Cancer Stage	Previous DREs Done by Urologist, %	Average Time Since Last Previous DRE, mo	Cancer Detected by Same Physician, %
B	35.0	14.7	77.8
C	34.5	16.6	89.5
D	36.5	28.3	57.9

TABLE 4.—*Time Since Primary Care Physician Did Last Previous Digital Rectal Examination (DRE)*

Cancer Stage	Previous DRE Done by Primary Care Physician, %	Average Time Since Last Previous DRE, mo	Cancer Detected by Same Physician, %
B	62.1	23.8	51.6
C	61.8	30.7	67.6
D	63.5	62.0	51.5

for stages B, C, and D, respectively). We compared the roles of the urologists and the primary care physicians in detecting prostate cancer by DRE (Tables 3 and 4). In all cancer stages, the average time since the last previous DRE was shorter when done by a urologist. In addition, in all stages the urologist was more likely to be the same physician who did the last previous DRE.

Discussion

An effective screening test for the early diagnosis of clinically significant prostate cancer is eagerly sought because of the poor prognosis of advanced disease and because a large percentage of the male population is reaching the at-risk age range. This has been an elusive goal, however. Mass screening of the asymptomatic male population for prostate cancer has not proved medically or economically justifiable. This is because of the high histologic prevalence of biologically insignificant tumors, the variable natural history, and the much lower incidence of clinically relevant disease. In one frequently cited study, nearly 6,000 men were examined by DRE over the course of 21 years, and in only 75 patients was prostate cancer detected.[25] Five-year survival for these patients was 77%, and it was noted that a subgroup of patients who received total prostatectomies had a higher five-year survival rate (91%) than men their age in the general population (83%). Major segments of the data were not reported, however, and the disease stages were omitted. Other studies report that screened cohorts are more likely to have more localized (stages A and B) cancer on diagnosis, but they can give no direct evidence that this leads to longer survival.[5,20,26]

Our data support the concept that periodic DRE leads to the discovery of carcinoma of the prostate in a more localized stage. Table 2 shows that the less time from the last previous DRE to the time of diagnosis, the more likely a localized, and thus more potentially curable, cancer would be detected. For instance, 77% of stage B and 74% of stage C patients had received a DRE within two years of detection, whereas 40% of stage D patients had not had a DRE within two years ($P < .05$).

Digital rectal examination alone is not a perfect test that reliably detects prostate cancer at an earlier stage—40% of our stage D cancer patients had had a screening DRE within 12 months of diagnosis. Serial DREs, however, do detect many prostate cancers when localized and thus more likely curable. The average interval between the last previous DRE and the detection of stage B cancer was less than two years but greater than four years in patients with stage D disease ($P < .056$) (Table 2). With stage B cancers being relatively curable by radical prostatectomy, stage C cancers being moderately curable by irradiation, and stage D cancers being incurable, the benefits of earlier detection are evident.

Our findings show that primary care physicians are proficient in detecting prostate cancer with the examiner-dependent DRE; 62.1% of stage B, 61.8% of stage C, and 63.5% of stage D tumors were detected by these physicians (Table 4). Urologists tend to follow their patients more closely with DRE than do primary care physicians. In addition, if the urologist was the person who did the diagnostic DRE, then he or she was more likely to be the physician who did the last previous DRE (Tables 3 and 4). Instruction in how and when to do a digital rectal examination should continue in our medical schools and primary care residency programs.

Perhaps the most critical question to be answered is, what would happen to the detection of prostate cancer if routine annual DREs were not performed? Without DREs, the only indication that prostate cancer was present would be by symptoms. Our data (Table 1) show that this is a poor method for the early detection of carcinoma of the prostate. Removing the DRE from the periodic physical examination would leave the detection of prostate cancer to only those patients with symptoms—and a strong likelihood that more advanced and incurable stage D disease was present.

In the strictest sense, the DRE has not been proved to enhance the quality and quantity of patients' lives. But this is far from being "not recommended," and omitting the DRE before other technologies are perfected is imprudent. This would reduce the early detection of not only prostate cancer but also some palpable rectal cancers, gastrointestinal disorders (by stool guaiac), neurologic disease (by sphincter tone), and other anorectal disease. The DRE is a low-cost, safe, established examination that can be done efficiently and effectively by primary care providers, is critical for the detection of early stage prostate cancers and other anorectal disease, and should remain part of the regular screening physical examination.

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TO PRONOUNCE THE DEAD

Every sleep shelters a dream
and in the white days
our need
is to worry the dream from its rest
though we live as if it were not so.

Our old minds
scratched dreams on the rock
and the granite faces wept
our dreams
with every rain washing
the quiet blind bones
we kept.
By heavier rains the bones
scattered and the rock
broke
and in long seasons of burning cherry
and holly hung with thorns
we painted our faces on boxes
and stray lengths of wood
as if these were mirrors
and we might fool our inside eyes
and dream
into the day.

Day comes
like a bright ship
boiling a long white wake that veils
the dreaming water
and the rune-reading of the veil
beguiles me till death
is a daily chore
and no more:
I walk
a long avenue of empty elms
their shadows stolen by the noon.
But no rune tells this:
that even within
the high white walls of noon
green sea-dreaming dragons make their kill
and on both shores of sleep their long waves lie
as even to the oyster pearling in the dark
must come the sand unbidden on the tide.

And so the dream must wake

and dreamless sleep it leaves behind
and night among the elms.

ANTOINETTE REED©
Palo Alto, California

Conferences and Reviews

The Clinical Diagnosis of Splenomegaly

JACK C. YANG, MD, MPH, *and* LELAND S. RICKMAN, MD, *San Diego, California, and* SONYA K. BOSSER, MD, *Bethesda, Maryland*

Assessing for the presence of splenomegaly is an important component of the physical examination. Although several methods of palpation and percussion of the spleen have been described, until recently they have not been validated by noninvasive imaging techniques such as ultrasonography, radionuclide scanning, and computed tomography that offer objective means to assess splenomegaly. We review the literature comparing various physical examination techniques with noninvasive imaging modalities and conclude that palpation and percussion of the spleen are complementary but frequently insensitive and that further studies are needed to evaluate the efficacy of specific diagnostic methods.

(Yang JC, Rickman LS, Bosser SK: The clinical diagnosis of splenomegaly. West J Med 1991 Jul; 155:47-52)

Since the recent development of sophisticated imaging techniques, some might consider the clinical impression of splenic size to be obsolete. The initial evaluation of a patient, however, still depends largely on the physical examination. The spleen normally lies in the left hypochondrium situated between the gastric fundus and diaphragm along the long axis of the left tenth rib. Its lower pole extends forward only as far as the midaxillary line.[1] Normal spleen weight varies with age, sex, body weight, and body surface area and can range from 58 grams in a 79-year-old woman to 170 grams in a 20-year-old man.[2] Insofar as its location should preclude palpation, a spleen that is detected on clinical examination may indicate the presence of disease and is likely to influence the choice of the differential diagnosis. Arkles and co-workers went to considerable length using scintigraphic scanning to conclude that "a palpable spleen is not necessarily enlarged or pathological" but conceded that "it is still important to exclude a pathological basis for this clinical finding."[3(p17)] Although the spleen was palpated in nearly 3% of healthy first-year college students,[4] splenomegaly should suggest a variety of infectious, neoplastic, or congestive disorders.[5]

Before the introduction of ultrasonography, radionuclide scintigraphic scanning, computed tomography (CT), and magnetic resonance imaging (MRI), physicians relied on examination techniques such as those described by Elmer and Rose in 1935. In *Physical Diagnosis*,[6] they apply the traditional principles of inspection, auscultation, palpation, and percussion. For example, splenomegaly may manifest as a left upper quadrant bulge on inspection, auscultation might uncover a venous hum suggesting congestion, and palpation and percussion may reveal solid tissue filling a space normally occupied by hollow organs.

Many modern texts on the physical examination offer terse descriptions of physical diagnostic techniques and fail to correlate or compare the various clinical methods for evaluating splenic size.[7-9] Because this information could affect the diagnosis and treatment, we review various clinical methods for detecting splenomegaly, noninvasive modalities for evaluating splenic size, and studies correlating the clinical assessment of splenomegaly with noninvasive imaging. Arteriography is considered an invasive modality and will not be discussed. Also, although the physical examination may aid in staging a disease (such as the lymphomas), a definitive diagnosis of splenic involvement for therapeutic purposes should still come from the tissue examination.

Methods of Physical Examination

Palpation

Three techniques for palpating the spleen are well known: bimanual palpation, ballottement, and palpation from above the patient. With bimanual palpation (Figure 1), the examiner's left hand is placed on the lower left rib cage and pulls the overlying skin toward the costal margin, allowing the fingertips of the right hand to sink under the ribs. The fingertips feel for the spleen's descent along the intercostal surface as the diaphragm contracts and descends with deep inspiration. The examination is repeated for the length of the costal margin and may be aided by having the patient lie partly on his or her right side.

The second technique is ballottement (Figure 2), which may be accomplished in the same position as the first. The examiner's left hand reaches over and around to the patient's left posterior chest wall and lifts, using the right hand to receive impulses that may be transmitted by an enlarged organ.

The third technique is done with the examiner at a supine patient's left shoulder (Figure 3). The patient places his or

Figure 1.—The spleen is palpated bimanually with the patient in a supine position and the examiner at the patient's right side. The examiner's left hand is placed on the lower left rib cage, and the right hand explores for the spleen.

From the Department of Surgery, University of California, San Diego, Medical Center (Dr Yang); the Division of Infectious Diseases, University of California, San Diego, Treatment Center (Dr Rickman); and the Department of Internal Medicine, National Naval Medical Center, Bethesda, Maryland (Dr Bosser).

Reprint requests to Leland S. Rickman, MD, Division of Infectious Diseases, UCSD Treatment Center, 2760 5th Ave, Ste 300, San Diego, CA 92103.

ABBREVIATIONS USED IN TEXT

CT = computed tomography
MRI = magnetic resonance imaging

her left fist beneath the back at the level of the 11th rib to push the spleen forward. The examiner then reaches over, curling his or her fingertips under the left costal margin, and palpates with the patient taking deep breaths.

Falsely abnormal ("false-positive") findings with palpation may occur in patients with flattened left hemidiaphragms due to chronic obstructive lung disease or in patients with prominent diaphragmatic excursions. Falsely normal ("false-negative") findings may occur in patients with obesity or ascites, narrow costal angles, a high diaphragm, or when another organ expands into the left upper quadrant.[10] A special circumstance exists when palpation may be relatively contraindicated, as in patients with infectious mononucleosis, in whom there is a small risk of splenic rupture with vigorous palpation.

Percussion

Nixon in 1954 described a method of detecting splenomegaly based on percussion (Figure 4).[11] The patient is placed on the right side so that the spleen lies above both the stomach and colon, thus permitting determination of both its upper and lower border of dullness. According to Nixon:

> Percussion is initiated at the lower level of pulmonary resonance in approximately the posterior axillary line and carried down obliquely on a general perpendicular line toward the lower midanterior costal margin. Normally the upper border of dullness is measured 6 to 8 centimeters above the costal margin. Dullness increased over 8 cm is indicative of splenic enlargement in the adult.[11]

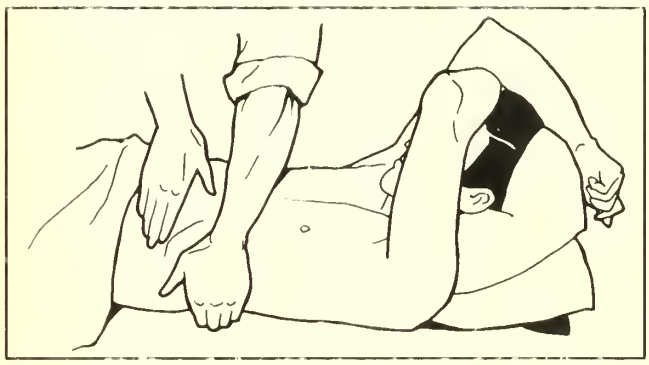

Figure 2.—The drawing shows the positioning of the examiner's hands during ballottement of the spleen.

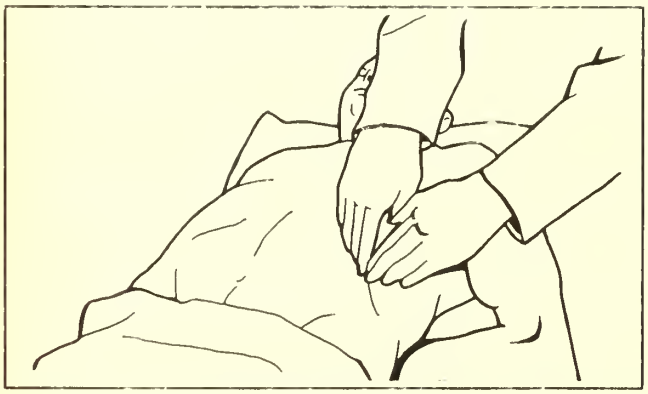

Figure 3.—The spleen is palpated from above.

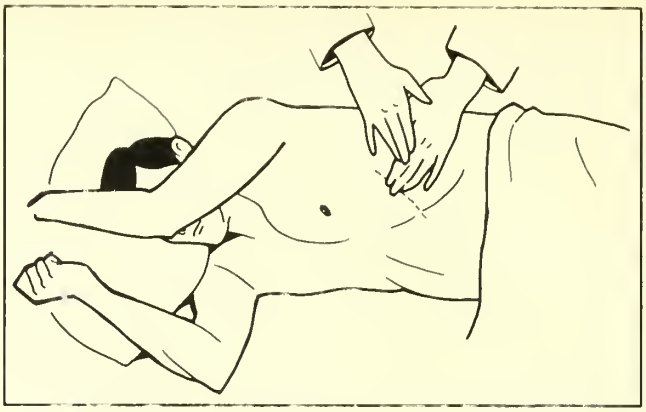

Figure 4.—The drawing depicts Nixon's method of percussing the spleen.[11]

In the original article, Nixon's method was confirmed in his experience "by successful splenic aspiration biopsies in 60 cases."[11]

Castell in 1967 published another method of percussion to detect splenomegaly (Figure 5)[12]:

> With the patient in the supine position, percussion in the lowest intercostal space (eighth or ninth) in the left anterior axillary line usually produces a resonant note if the spleen is normal in size. Furthermore, the resonance persists with full inspiration. As the spleen enlarges, the lower pole is displaced inferiorly and medially. This may produce a change in the percussion note in the lowest left interspace in the anterior axillary line from resonance to dullness with full inspiration. The percussion sign is considered positive, therefore, when such a change is noted between full expiration and full inspiration.

Although Castell's article is widely cited, the method described was validated in only ten male patients who had a positive percussion sign and a nonpalpable spleen, these findings being compared with those of a radioisotope scan using erythrocytes labeled with chromium 51. His ten "normal" controls were male patients with diseases in which hepatosplenomegaly was "not expected." Castell found that the mean spleen size was greater in patients with a positive percussion sign than in controls.

In another study, Castell and associates noted a difference in the estimation of liver size with light versus firm percussion, where light percussion correlated with the findings of a sonogram, but firm percussion tended to underestimate the liver size.[13] Whether, however, this difference in percussion technique is relevant to splenic examination is unknown.

A third method is percussion of Traube's semilunar space (Figure 6). Barkun and colleagues studied the sensitivity of this technique (discussed later)[14] and defined the borders as the left sixth rib superiorly, the left midaxillary line laterally, and the left costal margin inferiorly. Traube (1818-1876) recognized dullness over the usually tympanitic gastric air bubble as a sign of left pleural thickening in association with a tuberculous empyema.[15] Traube never clearly delineated the space that bears his name, nor did he associate left upper quadrant dullness with splenomegaly. Physicians today recognize that an enlarged spleen may displace Traube's space to the right of its defined position.[16]

Imaging Studies

Plain Radiographs

Roentgenographic examination can visualize the splenic shadow primarily because of its juxtaposition to gas in the stomach and the splenic flexure of the colon.

Whitley and co-workers in 1966 studied 81 routinely

taken abdominal films in which the spleen was seen and compared these with splenic weight by autopsy (done within eight weeks of the radiograph).[17] The best estimator of spleen weight in their study was the vertical length times the width of the spleen shadow at midpoint, with a correlation coefficient of .91. In general, however, plain films do not dependably outline the spleen and are mostly helpful only in cases of gross splenomegaly.[18-20]

Ultrasonography

The abdominal ultrasonogram is a safe, quick, noninvasive, and mobile method for assessing the splenic volume.

Kardel and associates in 1971 developed a method for calculating liver and spleen volumes based on parallel ultrasound scanning sections and compared these with the actual organ weights following splenectomy in nine patients suffering from hematologic diseases.[21] The correlation coefficient for their calculations was .98.

Niederau and colleagues in 1983 prospectively examined 915 healthy blood donors by ultrasonography.[22] They concluded that "longitudinal and transverse diameters are sufficient to estimate the size of the spleen, since both measurements correlate well with the diagonal diameter and cross-sectional area."[22(p540)] Other studies using similar simplified calculations in lieu of a more complicated integration of cross sections have also shown good results.[23-25]

On transverse sonograms of the abdomen, a rule of thumb has been that a normal-sized spleen does not extend anterior to an imaginary line drawn tangentially to the anterior border of the aorta and parallel to the back (Figure 7). Leopold and Asher, in the evaluation of more than 3,000 patients,[23] found this to be a generally reliable index in more than 90% of their subjects for determining the presence of splenomegaly. False-positive studies occurred with long, thin spleens that extended more anteriorly but were of normal volume. Although results obtained are often operator dependent, most ultrasound studies have shown both high sensitivity and specificity for the detection of splenomegaly.

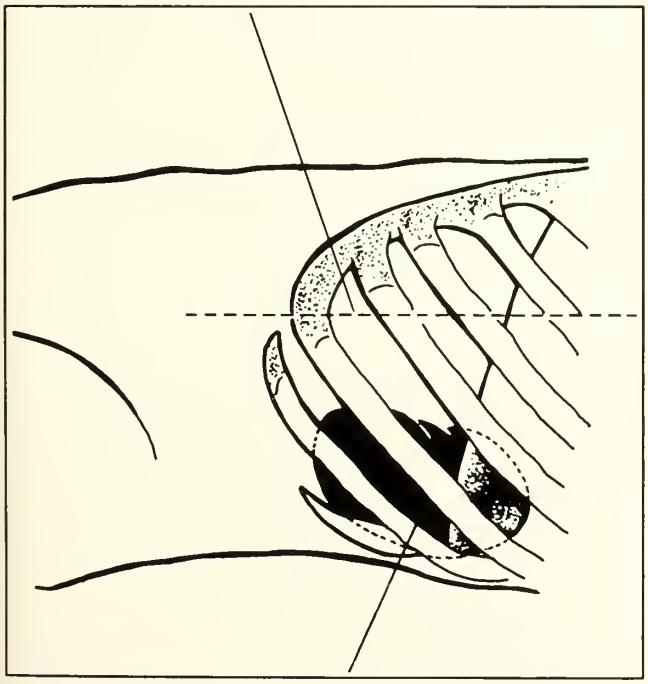

Figure 5.—In Castell's method[12] of percussing the spleen, the examiner percusses at the intersection of the left anterior axillary line and 9th intercostal space (marked). The lower diagonal line points to normal spleen.

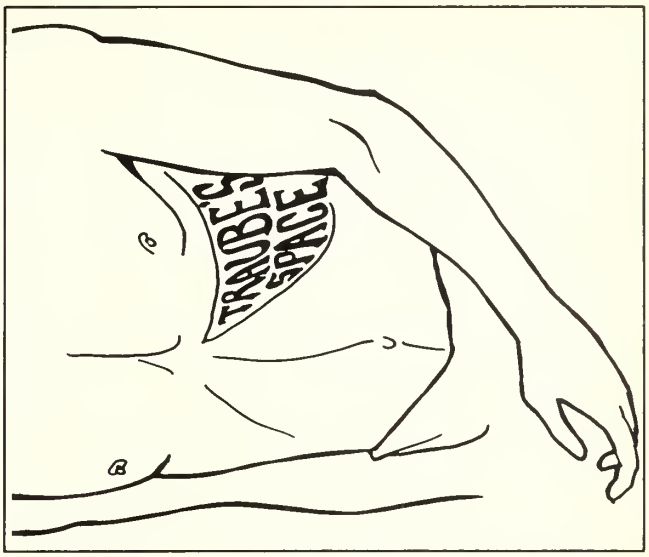

Figure 6.—Traube's space is shown, as defined by Barkun et al.[14]

Nuclear Scans

Several studies have shown radionuclide scanning to be accurate in predicting and assessing spleen size, but this method is limited by its immobility, relatively long total acquisition time, and cost. Also, its accuracy depends on the vascular integrity and function of the spleen.[26]

Holzbach and co-workers in 1962 used ^{51}Cr-labeled erythrocytes in 55 patients to determine splenic size.[27] Their subjects were 22 patients with cirrhosis and 23 controls without evidence of hepatic or splenic disease. In the other 10 cases, the spleen was examined postoperatively or at autopsy and the findings showed "good" correlation with scan activity (a correlation coefficient was not calculated).

Rollo and DeLand in 1970 estimated spleen mass from radionuclide images using technetium Tc 99m sulfur colloid and merisoprol Hg 197 in 21 patients, comparing the images with the actual mass obtained at postmortem examination.[28] Both posterior and left lateral images and then only posterior images revealed less than 13% error in all cases (mean error, 7%). In a similar study, Larson and associates, using ^{99m}Tc-sulfur colloid, scanned 26 "normal" control subjects

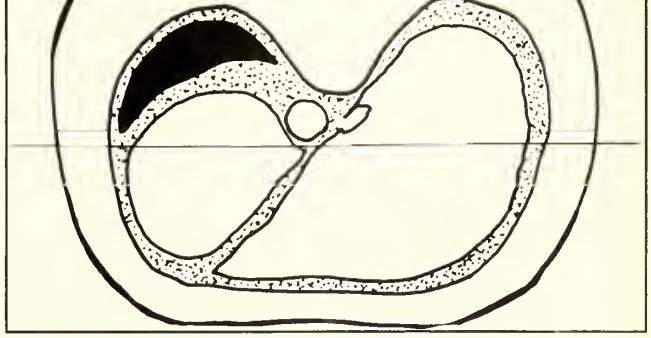

Figure 7.—In evaluating for the presence of splenomegaly with ultrasonography, a normal-sized spleen should not extend anterior to an imaginary line drawn tangentially to the anterior border of the aorta and parallel to the back (from Leopold and Asher[23]).

and 17 patients who either would undergo splenectomy (n = 14) or their spleens would be examined at autopsy (n = 3).[29] In their calculations, posterior length correlated best with actual weight ($r = .96$).

Using computed tomographs as standards, Strauss and colleagues found that the accuracy of in vivo nuclear scans was limited mostly by nonhomogenous tracer distribution and respiratory artifact caused by long acquisition times.[30]

One advantage unique to nuclear scanning has been in the detection of "ectopic," "aberrant," or "floating" spleens—that is, spleens that are not located in the left upper quadrant. In one case, both ultrasonography and CT scan delineated a large midabdominal mass that was thought to be a tumor until the colloidal uptake study showed the mass to be a congested, displaced spleen.[31] Nuclear scanning has also been effective in detecting accessory spleens in patients with recurrent immune thrombocytopenia.[32]

Computed Tomography and Magnetic Resonance Imaging

Neither CT nor MRI is limited by overlying ribs or aerated lungs and thus does not suffer some of the technical difficulties encountered with ultrasonography. In addition, the omental and mesenteric fat surrounding much of the spleen often permits a sharper demarcation of the capsule and hilar vasculature even without contrast media. Disadvantages with these methods include both that some patients cannot be transported to or placed on the scanner and the tests are expensive. Technical artifacts arise with motion and dynamic scanning.[33]

Heymsfield and co-workers in 1979 correlated the calculated mass from CT scans in two cadavers with the autopsy specimens of liver, kidney, or spleen[34] and found a mean difference of less than 5%.

Breiman and colleagues obtained CT scans in eight patients before splenectomy and predicted the spleen volumes using four mathematic integration techniques.[35] Using 1-cm spaced scanning produced a mean error of 3.59% and 2-cm spaced scans only 3.65%. Cools and associates sought to simplify calculations and retrospectively studied 50 abdominal CT scans.[36] Using only length and maximal width, they showed a correlation coefficient of .95 compared with previous methods of summing contiguous areas.

Stark and Bradley in their text on MRI note that "The diagnosis of splenomegaly is based on imprecise morphologic criteria analogous to CT."[37(p1123)] In addition, "Patients with hematologic disorders and splenomegaly generally show no consistent pattern of signal intensity alteration, and, except for enlargement, the spleen is unchanged on MR images."[37(p1123)] At this point, most believe MRI offers no clear advantage over CT in assessing splenic size.

Physical Examination Compared With Imaging

Palpation and Radiography

Dell and Klinefelter in 1946 and Blackburn in 1952 compared the results of physical examination with readings of plain abdominal radiographs, with the incorrect assumption that the radiograph would serve as a sensitive and objective standard.[38,39] Riemenschneider and Whalen invalidated those studies when they examined 47 spleens at autopsy and compared these with medical records of the physical examination and abdominal radiographs.[40] The authors concluded that neither palpation nor plain films were helpful in identifying splenomegaly.

Blendis and co-workers in 1970 also assessed observer variation in both clinical and radiologic examinations for hepatosplenomegaly.[41] They concluded that a plain film is a helpful adjunct to palpation in the assessment of hepatosplenomegaly because it is less subject to observer variation and is more easily quantifiable. This was one of the last studies of its kind because the new imaging modalities were just around the corner.

Physical Examination and Nuclear Scans

Holzbach and associates in their study of 55 patients using ^{51}Cr-labeled erythrocytes found 16 with enlarged spleens.[27] Of these patients, the spleen was palpated in 10, whereas the radiograph was judged to be abnormal in 8.

Sullivan and Williams in 1976 prospectively studied 65 patients about to undergo a ^{99m}Tc-sulfur colloid liver scan.[42] One examiner did percussion techniques described by Nixon and Castell,[11,12] as well as palpation with the patients in both the supine and right lateral positions. The criteria for splenomegaly on nuclear scan were longer than 12 cm and/or wider than 7 cm. Of 65 spleens, 17 were enlarged by scan. Of these, 12 were palpable (71% sensitivity), 10 were enlarged by Nixon's method of percussion (59% sensitivity), and 14 were enlarged by Castell's method of percussion (82% sensitivity). Overall, 14 of 17 cases of splenomegaly were detected by physical examination (88% sensitivity). The other 48 scans were considered normal, with 5 spleens palpable, 3 enlarged by Nixon's method, and 8 enlarged by Castell's method, for a cumulative false-positive rate of 16.6%.

Halpern and colleagues studied 214 patients who underwent liver and spleen ^{99m}Tc-sulfur colloid scans and reviewed the results of physical examinations in the patients' medical records.[43] In 92 cases of splenomegaly by scan, only 26 (28%) were detected on physical examination. False-positive

TABLE 1.—*Various Clinical Methods for Detecting Splenomegaly*

Examination	Reference	Sensitivity, %	Specificity, %	Comments
Palpation	Holzbach et al, 1962[27]	...	62	Compared with radionuclide scan (n=16); palpation method not described
	Halpern et al, 1974[43]	28	99	Review of 214 patient charts; method not described
	Sullivan and Williams, 1976[42]	71	90	65 patients examined by palpation, Nixon's method, and Castell's method before ^{99m}Tc-sulfur colloid liver scan
Percussion as described by				
Nixon*	Sullivan and Williams, 1976[42]	59	94	65 patients examined by palpation, Nixon's method, and Castell's method before ^{99m}Tc-sulfur colloid liver scan
Castell†	Sullivan and Williams, 1976[42]	82	83	65 patients examined by palpation, Nixon's method, and Castell's method before ^{99m}Tc-sulfur colloid liver scan
Traube‡	Barkun et al, 1989[14]	62	72	As compared with 118 patients who had had an abdominal ultrasonogram within 2 mo

*Nixon, 1954[11]
†Castell, 1967.[12]
‡As defined by Barkun et al, 1989[14]

TABLE 2.—*The Nonclinical Methods for Detecting Splenomegaly*

Examination	*Reference*	*Sensitivity, %*	*Specificity, %*	*r**	*Comments*
Plain film	Whitley et al, 1966[17]	...	...	.91	Compared with spleen weight at autopsy in films where the spleen was seen (n=81)
Ultrasonogram	Kardel et al, 1971[21]	...	...	.98	Compared with spleen weight after splenectomy (n=9)
	Koga and Morikawa, 1975[24]	~95	...	...	Patients with known liver disease (n=96)
	Leopold and Asher, 1975[23]	...	>90	...	"Observations in over 3,000 patients"
Nuclear scan	Rollo and DeLand, 1970[28]	~93	...	...	Using ^{99m}Tc and ^{197}Hg mean error=7%, compared with postmortem weight (n=21)
	Larson et al, 1971[29]	...	...	.96	Compared with weight at splenectomy (n=14) or autopsy (n=3)
	Strauss et al, 1984[30]	...	...	.87	Compared with CT in 47 patients
CT	Heymsfield et al, 1979[34]	>95	...	...	In situ CT in cadavers, then compared with autopsy weights (n=2)
	Breiman et al, 1982[35]	96.4	...	...	Mean error=3.6% compared with weights after splenectomy (n=8)
	Cools et al, 1983[36]	...	...	.95	Estimate based on simple linear measurements compared with previous method by Heymsfield et al (n=50)†; no true weights in study

CT=computed tomography

*r = Correlation coefficient.
†Heymsfield et al, 1979.[34]

results occurred in 3 cases (1.4%). This study is flawed, however, because a standardized method for physical examination was not established at the outset, which invalidates comparison with the scan. On the other hand, the chart data may reflect inadequately performed examinations, and many false-negatives could occur. Finally, nuclear scans are themselves subject to enough error (discussed earlier) to call their use into question as an objective standard.

Percussion and Ultrasonography

Barkun and associates sought to assess the clinical reliability of percussing Traube's space compared with ultrasonography.[14] Patients with known splenomegaly by ultrasonogram were matched with controls. By ultrasound examination, 43 of 118 subjects had enlarged spleens (length greater than 13 cm). Percussion of Traube's space yielded a 62% sensitivity and 72% specificity for the detection of splenomegaly.

Discussion

The clinical detection of splenic enlargement may be of great value in forming a differential diagnosis, whereas the erroneous assessment of splenomegaly may initiate an unnecessarily involved and invasive evaluation. Establishing the value of various clinical methods for detecting splenic enlargement has, in the past, been hindered by a lack of objective in vivo imaging. A summary of the various clinical methods for detecting splenography is given in Table 1. Although plain radiographs of the abdomen have been accessible for decades and may detect splenomegaly, the splenic outline is often difficult to visualize. The development of radionuclide scans and, more recently, of ultrasonography and computed tomography has made available more objective methods by which to evaluate the techniques of physical examination. The strongest of the early studies showed the relative accuracy of CT and ultrasonography compared with true weights obtained at splenectomy or autopsy. Various noninvasive modalities for the detection of splenomegaly are summarized in Table 2.

Both palpating and percussing the abdomen may detect splenomegaly. These techniques appear to be complementary, as each may fail to detect splenic enlargement. Ultrasonographic imaging is a noninvasive method well suited for the detection of splenic enlargement. Nuclear medicine scans appear to be fairly sensitive and specific for detecting splenomegaly, but these scans are more expensive and use radionuclides, which are prone to imprecisions. Computed tomography, although useful in evaluating splenic size and structure, exposes patients to ionizing radiation and sometimes contrast agents and is expensive. Both nuclear scans and CT suffer difficulties such as patient access and motion artifact causing distortion.

Detecting splenic enlargement is an important reason for doing a physical examination, but information on the relative efficacy of various clinical methods is either lacking or inadequate. With a low-cost, noninvasive, and accurate imaging technique such as ultrasonography, the techniques for splenic palpation and percussion can be readily evaluated in a controlled prospective study.

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Understanding Osteoporosis

ROBERT MARCUS, MD, *Palo Alto, California*

Considerable progress has been achieved recently in our understanding of the normal processes by which bone mass is regulated. Age-related trabecular bone loss is characterized not simply by a global loss of bone but also by cortical porosity and loss of trabecular connections. Because bone strength depends on architectural as well as material properties, bone quantity alone cannot define fracture risk with precision. Traditional therapies for osteoporosis increase bone mass, and estrogen therapy, in particular, profoundly decreases fracture risk. The pharmacologic restoration of bone quantity and quality, however, remains elusive. Modern biotechnology offers the hope that progress may come about through the development of growth factors and other osteotropic compounds for clinical use.

(Marcus R: Understanding osteoporosis. West J Med 1991 Jul; 155:53-60)

Among the characteristic changes in body composition that accompany normal human aging, the loss of bone continues to provoke interest and study. Osteoporosis is considered to be the end result of this loss and constitutes a major and growing public health problem for older women and men in Western society. Before the introduction of noninvasive bone mass measurements, osteoporosis was a clinical and radiologic diagnosis that could be made only after obvious skeletal damage had occurred. A diagnosis based on the presence of fracture proved unworkable because it was too restrictive, excluding persons whose bones were jeopardized but had not yet fractured. It is currently fashionable to define osteoporosis more inclusively as a critical reduction in bone mass to the point that fracture vulnerability increases. In this sense, osteoporosis is analogous to anemia defined as a low red blood cell mass. Although this is a useful definition, it introduces problems of specificity. A reduced bone mineral content does predict fracture risk[1-4] but accounts for only a portion of this risk, so issues beyond simple mineral content must be operative. In this article I will summarize the mechanisms by which bone mass is acquired and maintained through life and the structural characteristics, prevention, and treatment of established osteoporosis. To assist readers to understand these many contributions to skeletal health, I shall begin with a brief review of skeletal organization and functional behavior.

Skeletal Organization

The skeleton can be considered as two compartments, peripheral and central. The peripheral skeleton constitutes 80% of skeletal mass and is composed of compact plates, or lamellae, of cortical bone organized about central nutrient canals. Bones of the central, or axial, skeleton consist of trabecular or cancellous bone contained within a thin cortical shell. Trabecular bone is a honeycomb of vertical and horizontal bars filled with red marrow and fat. It is localized for the most part in the vertebral bodies, the pelvis, and the proximal femur. The metaphyseal ends of long bones also contain trabecular bone but no red marrow in the adult. Vertebral bodies contain about 35% trabecular bone by weight[5] and about 70% by volume, which greatly exceeds the trabecular component of peripheral bones. The increased surface area of trabecular bone accounts for the fact that changes in bone mass due to altered turnover occur earlier and are more impressive in the axial skeleton.

Bone Remodeling

Bone participates in three fundamental activities: Modeling refers to the process by which the characteristic shape of a bone is achieved. Repair is the regenerative response to fracture. Remodeling is a continuous cycle of destruction and renewal that is carried out by individual, independent "bone remodeling units," illustrated in Figure 1.

Normally 90% of bone surfaces are at rest, covered by a

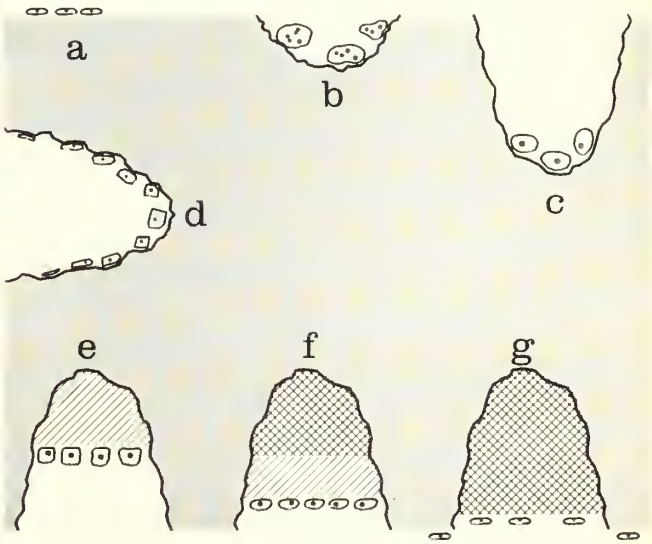

Figure 1.—The bone remodeling cycle is shown: **a**, resting trabecular surface; **b**, multinucleated osteoclasts dig a cavity of approximately 20 μm; **c**, resorption to 60 μm is completed by mononuclear phagocytes; **d**, osteoblast precursors are recruited to the base of the resorption cavity; **e**, new matrix is secreted by osteoblasts; **f**, matrix continues to be secreted, with the initiation of calcification; and **g**, mineralization of the new matrix is completed. Bone has returned to a quiescent state, but a small deficit in bone mass persists (from Marcus,[6] with permission).

From the Geriatric Research, Education and Clinical Center, Veterans Affairs Medical Center, Palo Alto, and the Department of Medicine, Division of Gerontology, Stanford University School of Medicine, Stanford, California.

Reprint requests to Robert Marcus, MD, Geriatric Research, Education and Clinical Center, VA Medical Center, 3801 Miranda Ave (182-B), Palo Alto, CA 94304

thin layer of inactive lining cells. Remodeling is initiated by hormonal or physical signals that cause marrow precursor cells to cluster on the bone surface where they fuse to become multinucleated osteoclasts and dig a cavity into the bone. In cortical bone this appears as a resorption tunnel within a haversian canal. On trabecular surfaces it is a scalloped area called a Howship's lacuna. The resorption front leaves a cavity about 60 μm deep. The extent of deepest resorption appears as a cement line, a region of poorly organized collagen fibrils, as opposed to the osteon itself, which shows lamellar collagen deposition.

Coupled to resorption, bone formation ensues when a local release of chemical mediators attracts preosteoblasts into the resorption cavity. These mature into osteoblasts that replace the missing bone by secreting new collagen and matrix constituents. Matrix production is initially rapid, the new osteoid seam approaching 20 μm in thickness when mineral deposition begins. With time, mineralization catches up to matrix deposition, and the new bone becomes fully mineralized. Resorption and formation are complete within 8 to 12 weeks, several additional weeks being required to complete mineralization.

If the replacement of resorbed bone were completely efficient, bone would be restored to its initial state at the end of a remodeling cycle. Remodeling, however, like most biologic processes, is not entirely efficient, so that a small bone deficit persists on completion of each cycle. The consequence of this inefficiency is that age-related bone loss is a normal, predictable phenomenon, beginning shortly after the cessation of linear growth. Alterations in remodeling activity represent the final pathway through which diverse stimuli, such as dietary or hormonal insufficiency, affect the rate of bone loss. Alterations in the overall bone remodeling rate can reflect several distinct alterations in the components of the remodeling cycle. These include a change in the activation, or birthrate, of remodeling units, the resorptive capacity of individual units, or in the magnitude of the bone formation response.

Because bone remodeling leads to progressive bone loss, we may ask what useful function it serves. Current evidence suggests that remodeling fulfills a scavenger role by which areas of fatigue microdamage are removed and replaced by intact lamellar bone. Although the inefficiency of this process may diminish bone mass and strength in the long run, short-term protection against routine wear is provided. For a more detailed discussion of bone remodeling, readers are referred to a review published elsewhere.[6]

Changes in Bone Mass With Age

Peripheral Skeleton

It has become axiomatic that bone is lost with aging. The traditional view of this process was clearly enunciated by Garn and co-workers, whose careful radiographic measurements of metacarpal cortical thickness described a characteristic trajectory of bone mass throughout life.[7] By this model, bone mass is gained during adolescence, reaches a plateau during the third decade, and remains stable until about age 50, after which progressive loss occurs. A similar trajectory was observed for men and women and for all ethnic groups. This model has been repeatedly confirmed by newer, noninvasive methods, and has been extended by the observation that the initial loss of bone at age 50 is temporarily more rapid in women, presumably because of the menopause.[8]

Axial Skeleton

Pioneering studies with postmortem specimens suggested that the loss of axial bone begins earlier than that of cortical bone,[9,10] a view that has been confirmed by absorptiometry and biopsy. Although there is consensus that an early loss of trabecular bone occurs, controversy persists over its timing, the presence of menopausal acceleration, and whether all regions of trabecular bone are similarly affected. Biopsy results document a significant premenopausal decline in trabecular bone mass of the iliac crest that appears to begin as early as the third decade,[11-14] with a predicted rate of bone loss of about 0.7% per year. At that rate, the cumulative bone loss over a span of 30 years could amount to 25% of the original trabecular bone volume even before menopause is reached.

Densitometric measurements of the spine have been variably interpreted to suggest linear and nonlinear loss of bone with age. Madsen and Riggs and associates described a single negative correlation of lumbar spine mineral with age, with a slope in women of about 1% per year.[15,16] Men also lost bone with age, but the slope was less than half that observed for women. Other absorptiometric data have varied, some in support of early axial loss and some failing to show such a change.[17] These discrepancies are not understood but may reflect the cross-sectional nature of these studies and the fact that the sample size for detecting subtle changes in the regression slope exceeds that of any reported study.

Most densitometric studies suggest a transient period of accelerated bone loss at[18-21] or a few years immediately before menopause.[22,23] In their original cross-sectional study, Riggs and colleagues did not demonstrate menopausal acceleration at the lumbar spine,[16] a result that they confirmed in a longitudinal examination of the same question.[24] The reasons for this discrepancy are not clear.

Peak Bone Mass

Bone density and fracture risk in later years are determined not only by the rate of bone loss during adult life, but also by the maximal bone mineral content at skeletal maturity, called the peak bone mass. Only recently has serious attention been given to understanding the acquisition of peak bone mass. It has been frequently stated that bone mass reaches a maximum just before the onset of trabecular loss, sometime during the third decade, but recent data suggest that axial bone mass reaches a maximum earlier, perhaps in late adolescence.[25]

Many factors determine peak bone mass. Inheritance appears to account for 70% or more of the variance in bone mass in healthy young women. Other independent predictors include muscle strength, physical activity, circulating estrogen and androgens, and dietary calcium.[26-28]

Constraints on the Relationship Between Mineral Density and Bone Strength

Most patients with osteoporotic fractures have low bone density compared with age-matched nonfractured control subjects. This is not surprising in view of the close relationship between bone mineral density and strength.[29] Major overlap is seen, however, in the bone densities of fracture patients and controls regardless of measurement technique. In prospective studies,[2-4] progressive increases in fracture

incidence can be shown as levels of bone mass decrease. For example, persons in the lowest quartile of bone mineral content may have a twofold to threefold increase in the incidence of hip fracture over time.[3] Here again, however, many people in that category may never actually sustain a fracture, so fracture risk must also depend on factors beyond simple bone mineral density. Extraskeletal factors such as the susceptibility to falls have been frequently discussed. Less commonly appreciated are skeletal factors other than global bone mineral density that influence bone competence. These include bone material and geometric properties. The material properties include the brittleness and ultimate breaking strength of the bone. Although mineral content is a primary determinant of material properties, factors such as the accumulation of cement lines over time, crystal maturation, and changes in collagen cross-linking may all diminish bone strength with age.

The major geometric influence on the competence of long bones is the distribution of bone mass about its bending axis. This can be expressed mathematically as a term called the cross-sectional "moment of inertia." Briefly summarized, the farther away the mass of an object is located from the central bending axis, the greater is its strength. An interesting example of this phenomenon in men is age-related expansion of the femoral diameter. Here an increase in the moment of inertia compensates for the loss of mass and maintains bone strength. This compensation appears not to occur in women.[30,31]

In the axial skeleton, changes in the trabecular microstructure are highly relevant to fracture risk. In young people, trabecular bone consists of thick vertical plates that are connected by thinner horizontal trabeculae. Parfitt and co-workers and Weinstein and Hutson showed that the space between adjacent trabeculae increases with age, reflecting the loss of entire trabecular elements.[32,33] They suggested that this loss was the result of trabecular perforation during resorption. Presumably, perforated trabeculae offer no scaffold for new bone formation to take place. Thus, the loss of trabeculae with age leads to deficient horizontal trabecular connections, the consequence of which is a substantial decrease in the capacity of vertical trabeculae to withstand bending stress.

The role of trabecular connectivity is central to understanding why measurements of bone mineral density do not adequately predict fracture risk. Two people may have the same low mineral density; in one, this reflects diffusely thin trabeculae with the maintenance of normal trabecular connections, and the other shows porous bone with reduced trabecular connections. The first person may have a trivial fracture risk, whereas the bones of the second person may be in extreme jeopardy. Current noninvasive tools for the clinical assessment of bone mass do not distinguish between these two situations. Until methods are developed to make such distinctions, the usefulness of bone density measurements to predict individual fracture risk will be limited.

Mechanisms of Bone Mass Regulation

Alterations in remodeling dynamics are the common mechanism by which bone mass is regulated. Primary regulators include physical activity, reproductive endocrine status, and calcium nutriture. The contributions of these three areas to bone mass are summarized here.

Physical Activity

Although the mechanisms remain to be elucidated, bone adapts to the loads applied to it (Wolff's law), giving rise to the view that increased physical activity is a potential means to improve bone mass.[34] This adaptation includes an increase in density when mechanical loading increases and a loss of bone density when customary loads are removed. The loss of bone with immobilization, such as with spinal cord injury, is a frequent and challenging clinical problem. The loss of bone with extended space flight emphasizes the critical role of gravitational stress to the maintenance of bone mass.[35] Rubin and Lanyon found that applying physiologic loads to isolated turkey ulnae increased the bone area after a few weeks.[36,37] The maximal effect of loading was achieved by a relatively small number of load cycles, and substantial increases beyond that point promoted no additional increase in bone mass. Based on a mathematical model, Whalen and colleagues predicted that load magnitude was a more important determinant of bone density than the number of load cycles.[38] Applied to exercise training, this model predicts that resistance exercise, such as weight training, would be a better stimulus for increasing bone mass than would an endurance exercise like jogging, in which repetitions are the primary training stimulus.

Because muscle contraction is the dominant source of skeletal loading, it is not surprising that significant relationships exist between indices of bone and muscle mass[39] and between bone mineral density and muscle strength at specific sites.[28,40,41]

There is strong support for the notion that the bone mass of athletes exceeds that of sedentary persons.[34] Not only is bone density higher in physically active people, but increased activity may slow age-related bone loss. One must interpret these cross-sectional analyses with caution because genetic and musculoskeletal characteristics may distinguish "athletic" from "sedentary" persons even before exercise training is initiated. A few intervention trials have examined the effects of exercise on bone density. Once again interpretation requires caution because most of these studies have not been randomized trials; several have involved training routines suited for cardiovascular fitness but perhaps inappropriate for skeletal loading. Nonetheless, the results generally confirm that bone density increases with exercise training.

Dalsky and co-workers reported an increase in spinal bone mineral content after nine months of resistance exercise by elderly women.[42] In contrast, Cavanaugh and Cann found that postmenopausal women lost mineral from the spine during a one-year program of brisk walking.[43] These contradictory results give insight into the type of exercise that is required for an osteogenic response. Dalsky and associates' exercise group jogged and walked but also did a series of resistance exercises, such as rowing, that specifically load the vertebrae. In contrast, the Cavanaugh and Cann protocol included only walking. The forces produced at the lumbar vertebrae during fast walking and jogging are 1 and 1.75 times body weight, respectively, whereas resistance activity applies lumbar vertebral stresses as high as 5 to 6 times body weight. Thus, these data suggest that resistance exercise is more potent than brisk walking in preserving bone mass. This notion, if validated, carries important therapeutic implications because weight-bearing exercise, defined as walking, jogging, running, and dancing, has been the form of activity

traditionally prescribed for skeletal benefit. Although serious weight-loading of frail elders might not be safely carried out, the results of Dalsky and colleagues lend optimism that lower intensity resistance training could be successfully introduced in this population. The primary benefits of high weight-loading exercise would accrue to teenaged and young adults who are still acquiring bone mass and whose spines could tolerate loading with minimal fracture risk. Recent experience indicates that these benefits, although significant, may be relatively modest. Gleeson and co-workers trained a group of premenopausal women with a progressive resistance program.[44] Exercises were carried out with good compliance and substantial gains in strength. After a year of training, the weight lifters showed an average increase in spine mineral content of 0.82%. Thus, for major gains in bone mass to be achieved by resistance exercise, training regimens may exceed the capacity of most people.

Another insight from the work of Dalsky and colleagues was the observation that bone mass returned toward baseline levels in subjects who stopped the training regimen.[42] Thus, for exercise programs to deliver long-term skeletal benefits, they must be sustained. Furthermore, because bone mass eventually reaches a steady-state level appropriate to its habitual mechanical loading, continued improvement in bone mass will occur only if the level of exercise also continues to increase.

Calcium Nutritional State

The skeleton contains 99.5% of body calcium stores. It provides a mineral reservoir to support plasma calcium levels at times of need. Published explications of the relationship of dietary calcium to skeletal integrity are complex and will not be detailed here, but a few summary statements are in order.

The recommended dietary calcium intake for adolescent boys and girls is 1,200 mg a day, a figure derived primarily from balance studies. Because the two or three years that define the pubertal growth spurt are accompanied by the deposition of 60% of final bone mass, dietary inadequacy limits bone formation far more at this time than at other times of life. Consumption figures indicate that the calcium intake of American men corresponds reasonably well to the amounts recommended for most ages but that median intakes for girls are well below target levels by age 11 and never recover.[45] Thus, calcium undernutrition probably has an important influence on peak bone mass in women.

During the third through the fifth decades, growth has stopped and robust compensatory mechanisms permit a rapid adaptation to even severe dietary restriction. It should not be surprising that the calcium nutritional state appears not to affect the rate of bone loss during this period,[24] and, therefore, it is unlikely that calcium supplementation will exert important beneficial effects on bone mass at this time. It is ironic that this population receives the greatest portion of calcium supplement advertising.

At menopause, accelerated bone loss reflects a loss of endogenous estrogen and has little relationship to dietary calcium intake. Riis and associates showed only modest effects on bone loss when early-menopausal women were given extra calcium.[46] Habitual dietary calcium intakes of Danish women average 1,100 mg a day, however, which is considerably higher than in the United States, so what may have been a marginal effect in Denmark might be more substantial in North America.

After age 60, the early effects of estrogen deficiency have dissipated, and the compensations to accommodate dietary inadequacy are less efficient. At this time, proper attention to calcium intake, be it from diet or supplements, is rational and has been shown to have beneficial effects on bone turnover and mass.[47]

Endocrine Reproductive Status

Formidable evidence supports a critical role for gonadal function in the acquisition and maintenance of bone mass. Hypogonadal boys and girls show important deficits in cortical and trabecular bone mineral, and a loss of endogenous androgen or estrogen during adult life leads to an accelerated loss of bone mineral. In women, the loss of estrogen has dual effects. Decreased efficiency of intestinal and renal calcium handling increases the calcium requirement.[48] Recent evidence shows that estrogen directly affects bone cell function,[49,50] and this interaction may underlie the accelerated bone loss of early estrogen deficiency. In terms of bone remodeling, estrogen deficiency permits osteoclasts to resorb bone with greater efficiency. This may lead to trabecular perforation. Estrogen replacement at menopause protects bone mass and affords significant protection against osteoporotic fractures.[51-55] The degree to which this protection reflects direct actions of estrogen on bone cells is not known, as estrogen replacement also increases circulating levels of 1,25-dihydroxyvitamin D, improving the efficiency of intestinal calcium absorption in menopausal women.[56,57]

The skeletal role of androgens is less well understood. Testosterone deficiency is a major cause of osteoporosis in men, in whom replacement therapy restores bone mass. Specific testosterone receptors have been recently shown in normal human osteoblasts.[58] Whether direct actions on bone cells fully account for the effects of androgen on bone mass is unknown. Androgen therapy also increases muscle mass, so effects on bone may be due to the increased mechanical loading that would accompany increased muscle bulk. Finally, circulating androgens make an important contribution to peak bone mass in women.

It needs to be emphasized that the optimal acquisition and maintenance of bone require sufficiency in all areas: physical activity, reproductive status, and nutrition. Deficiency in one is not compensated by excessive attention to another. Women athletes who become hypogonadal lose bone despite frequent high-intensity exercise.[59,60] Therapeutic specificity is a venerable medical tradition. Just as it would be inappropriate to treat iron deficiency with folic acid, it is equally futile to prescribe calcium to an immobilized patient or to prescribe exercise and calcium rather than giving estrogen at menopause.

Osteoporosis

In 1948 Albright and Reifenstein concluded that osteoporosis comprised two separate disorders, one related to menopausal estrogen loss and the other to aging.[61] Recent support for this concept has been published by Riggs and associates, who proposed that "primary" osteoporosis represents two fundamentally different conditions[62]: type I osteoporosis, the loss of trabecular bone after menopause; and type II osteoporosis, the age-related loss of cortical and trabecular bone in men and women. Whereas the type I disorder is theoretically related to a lack of estrogen, type II osteoporosis would reflect long-term remodeling efficiency,

dietary adequacy, and intestinal and renal function. Compelling proof that these two disorders are truly distinct remains to be obtained. Iliac crest biopsy specimens from women with type I osteoporosis showed no consistent or unique histomorphometric features.[63] It has been widely assumed that osteoporosis must reflect excessive bone loss, but some patients with apparent type I osteoporosis on the basis of vertebral compression and a low axial bone mass for age may have inadequate bone acquisition rather than excessive loss. It is also possible that differences in fracture patterns from one patient to the next are more indicative of the tendency to fall and the types of falls that are experienced rather than fundamental differences in bone physiology. Resolution of this issue will require additional longitudinal study. Although many osteoporotic women undoubtedly have excessive menopausal bone loss, it may be more appropriate to consider osteoporosis as the result of multiple physical, hormonal, and nutritional factors acting alone or in concert rather than to become wedded to an unvalidated theoretic model.

Preventing Osteoporosis

A rational strategy to prevent osteoporosis follows from the considerations outlined earlier. Regular physical activity of a reasonable intensity can be endorsed for all age groups. For growing children and adolescents, adequate attention to dietary calcium is important if their peak bone mass is to reach the level appropriate for genetic endowment and habitual mechanical loading. Further attention to nutritional support may be required in the seventh decade and beyond in the form of increased food calcium or calcium and vitamin D supplementation. For women at menopause, the timely administration of estrogen is the most powerful intervention for preserving bone mass and protecting against fracture. Indeed, at any age, preventing or correcting hypogonadism is an important consideration. No therapy or combination of approaches can guarantee freedom from osteoporotic fracture, but with appropriate lifelong attention to physical activity, nutritional state, and reproductive hormone status, important reductions in subsequent fracture risk can be achieved.

Treating Established Osteoporosis

In this section I use the term "established osteoporosis" to indicate the condition in patients who have sustained at least one nontraumatic fracture of the spine, forearm, or hip. This usage avoids the question of whether a person whose bone mineral density is 1 or 2 standard deviations below predicted levels necessarily has bone fragility. As discussed, a decreased bone mass is associated with increased fracture risk but even at low levels does not necessarily lead to fractures. It is premature to recommend treatment—as opposed to preventive intervention—based simply on bone mass determinations in patients who have not sustained a fragility fracture.

Pharmacologic approaches to managing osteoporotic patients fall into two groups (Table 1). The first consists of agents that constrain the rate of bone loss. These are thought to work primarily by decreasing the rate of bone resorption and are frequently referred to as "antiresorptive" agents. The second group consists of agents that promote bone formation.

TABLE 1.—*Pharmacologic Approaches for Osteoporosis*

Drug Class		
Antiresorptive	*Bone Forming*	*Experimental*
Estrogen	Fluoride	Growth hormone (IGF-I)
Calcitonin	Androgen	TGF-β
Bisphosphonate	Parathyroid hormone	Coupling factors
		Sequenced therapy (ADFR)

ADFR = "activate-depress-free-repeat," IGF-I = insulinlike growth factor I, TGF-β = transforming growth factor-β

Antiresorptive Agents

Estrogen. The effects of estrogen on the maintenance of bone mass and fracture protection were outlined earlier. The minimal effective dose of estrogen as sole therapy is 0.625 mg per day of conjugated equine estrogens or its equivalent. Both oral and transcutaneous estrogen reduce biochemical evidence of bone turnover. Although both should provide adequate protection against fracture, experience with transcutaneous hormone is fairly recent, and its effect on fracture is not known. The cessation of estrogen leads to an acceleration in bone loss, so therapy, once initiated, should be long term. Protection against hip fracture may require at least five years to emerge.

Standard practice recommends the cyclic or continuous administration of progestational drugs to women with an intact uterus. The C-21 progestins (such as medroxyprogesterone acetate) appear not to interfere with the skeletal effects of estrogen. The androgenic progestins (such as norethindrone) may actually preserve bone mass by their own accord and may provide added skeletal benefits when given with estrogen.

Calcitonin. This peptide hormone is a powerful inhibitor of osteoclastic bone resorption and is associated with modest increases in bone mass in patients with osteoporosis.[64,65] These increases are most impressive in patients whose intrinsic rate of bone turnover is high and in such patients may approach 10% to 15%, after which a plateau is reached. It is likely, therefore, that they represent simple reductions in the labile deficit of bone called the "remodeling space," which is an overall reflection of remodeling activity. Because bone resorption and formation are normally coupled, the long-term use of calcitonin will lead ultimately to a reduction in bone formation. Calcitonin has not been shown to decrease the risk for osteoporotic fracture. Two disadvantages with calcitonin use are its expense and that it requires parenteral injection. A preparation of calcitonin suitable for nasal administration should be available soon. Many women are unable or unwilling to accept estrogen replacement on entering menopause. In this setting, the use of calcitonin has been shown to provide a reasonable preservation of bone mass.

Bisphosphonates (diphosphonates). These drugs represent another category of medications that are primarily antiresorptive. The sole bisphosphonate currently available in the United States is etidronate disodium (Didronel), which has been used in the management of patients with Paget's disease of bone. In two recent randomized intervention trials, it was found that the cyclic use of etidronate—400 mg per day for two weeks, followed by three months off therapy—achieved modest increases in bone mass over several years, and that these increases were associated with a significant reduction in vertebral fracture compared with those in a placebo group.[66,67] Although its cyclic nature may reduce the long-term consequences of bisphosphonate use, the sustained use of etidronate has been associated with osteomala-

cia in patients with Paget's disease, so additional studies must be carried out before its long-term role will be understood. Nonetheless, results to date are encouraging, and it appears that the cyclic use of bisphosphonate will be a useful therapy.

Although it is premature to render definitive views on the ultimate role for bisphosphonates, it is reasonable to ask whether this approach constitutes a satisfactory alternative to estrogen. My view is that bisphosphonates are not equivalent to estrogen, and women who can take estrogen should be encouraged preferentially to do so. Although etidronate use has reduced the short-term incidence of vertebral compression fracture, in contrast to estrogen, it has not been shown to decrease the risk for hip or other peripheral bone fractures. It is interesting to speculate whether adding etidronate to estrogen therapy may confer added benefit, but there is no published information regarding this. Many patients who cannot or will not take estrogen might benefit from the use of bisphosphonate. These include women with a history of breast cancer and men. Reports of studies of these particular groups can be anticipated in the near future.

Thiazide diuretics. Although not strictly antiresorptive, thiazides reduce urinary calcium excretion and help constrain bone loss in patients with hypercalciuria. Whether they will prove useful in patients who do not have hypercalciuria remains to be established, but recent epidemiologic data suggest that they provide significant protection against the risk for hip fracture.[68]

Bone-Forming Agents

Fluoride. It has been known for many years that the administration of sodium fluoride, in doses of 30 to 60 mg per day, can increase trabecular bone mass in many patients. Until recently, much of the fluoride literature has been anecdotal or retrospective, not based on properly controlled therapeutic trials. Such literature has been interpreted to show that fluoride use provides substantial vertebral fracture protection. Two prospective clinical trials cast serious doubt on this interpretation. Riggs and Kleerekoper and colleagues conducted randomized, double-blind, placebo-controlled protocols in which bone mass and fracture occurrence were monitored over several years.[69,70] Although fluoride use was associated with notable increases in lumbar spine mineral density, neither study showed any protective effect against vertebral compression fractures. In addition, the study of Riggs and co-workers showed a significant increase in the occurrence of peripheral fractures and stress fractures in the group taking fluoride.[69] These studies might be criticized for the high dose of fluoride that was used (75 mg per day), and French workers in a prospective trial reported that 30 to 50 mg per day of sodium fluoride was associated with a decreased fracture risk.[71] The results of Riggs and Kleerekoper and associates, however, clearly show that increased bone mass is not synonymous with increased bone strength and that if any dose of fluoride proves useful, there is a fairly narrow therapeutic window.[69,70] It is incumbent on the advocates of fluoride treatment to show its efficacy and safety in properly controlled clinical trials. Until that has been done, the general use of fluoride cannot be recommended.

Androgen. Testosterone deficiency is a major etiologic factor for osteoporosis in men, and replacement therapy notably increases bone mass in such patients. In addition, the long-term administration of androgens significantly increases bone mass in osteoporotic women, but therapy has been limited by virilizing side effects. Several reports suggest that nandrolone decanoate, 50 mg administered intramuscularly every three weeks, increases peripheral and axial bone mass without bothersome side effects in osteoporotic women.[72] Adequate fracture data are not yet available, so it is impossible to make a judgment on the therapeutic role for this therapy. In view, however, of the potential benefits to muscle as well as bone, in addition to its possible deleterious effects on lipoprotein metabolism and circulating levels of high-density-lipoprotein and low-density-lipoprotein cholesterol, androgen clearly deserves additional careful study.

Experimental Approaches

It can be seen from this discussion that standard therapies, such as estrogen, calcium, and exercise, are successful primarily in maintaining rather than increasing bone. Agents that stimulate new bone formation are either problematic or still experimental, and effective strategies to increase bone mass in patients with osteoporosis remain elusive. Thus, there has been considerable interest in developing new approaches to increase bone mass. An area of great excitement has been to manipulate the components of bone remodeling to achieve the optimal stimulation of bone formation. Frost and others described methods to exploit the separate components of the bone remodeling cycle in sequence.[73] This approach, called "activate-depress-free-repeat" or "coherence therapy," has great theoretic interest but has been applied only casually to date. In these protocols, agents that increase the synchronous birthrate of active remodeling units, such as parathyroid hormone, inorganic phosphorus, calcitriol, or triiodothyronine, are given for several days, followed by compounds such as bisphosphonate or calcitonin that inhibit osteoclast function and diminish resorption. This "depression" phase is followed by a drug-free interval to permit the completion of bone formation, and the cycle is repeated. It is hoped that the combination of stimulated remodeling and constrained resorption will allow bone formation to generate more bone than had been previously removed. Encouraging results have been reported,[74,75] but the ultimate usefulness of this approach remains uncertain. One major problem with coherence therapy is that the regimens used have all been developed in a completely empiric manner. The dose and timing of remodeling initiators necessary to commit a coupled bone formation response are unknown. Whether the early administration of antiresorptive drugs attenuates the osteoblastic response appears to be an important question, but no published information is available on this point.

Various peptide hormones and biologic agents show potential in treating osteoporosis. Parathyroid hormone, given as sole intermittent therapy, increases trabecular bone mass.[76] Transforming growth factor-β has not been used in treatment protocols, but its use is attractive because it inhibits bone resorption and increases bone formation. Recombinant human growth hormone has been shown to elevate circulating levels of osteocalcin,[77,78] a marker of bone formation. Thus, growth hormone or its surrogate, insulinlike growth factor I, might also be useful to increase bone mass.

Nonpharmacologic Considerations

A number of measures may be of use in reducing the risk of fracture for osteoporotic patients. Proper instruction in lifting technique may reduce strain on the spine. Proper footwear and the installation of safety features around the home

may minimize the risk of falling. Such features include bathroom safety rails and night-lights, rails and lighting for stairways, and the elimination of floor clutter. In most areas, home safety inspections by public health nurses can be arranged easily.

Conclusions

In recent years considerable progress has been achieved in our understanding of the normal processes by which peak adult bone mass is acquired and maintained; the physical, nutritional, and hormonal factors that regulate bone mass throughout adult life; and the critical role of reproductive hormonal replacement for maintaining bone mass within the early years after menopause. Moreover, it is now apparent that a loss of bone quantity is not sufficient to explain increased fracture risk. Bone fragility depends not only on its material properties, of which mineral content is an important component, but also on its microarchitecture and geometry. Age-related trabecular bone loss is manifest not simply as a global loss of bone mass but is characterized by a loss of trabecular connectivity and increased porosity.

Traditional treatment modalities include estrogen, calcium, and exercise. Each shows substantial benefit on bone mass, and estrogen, in particular, exerts a profound influence on fracture risk. None of these, however, has been shown to restore the bone mass of osteopenic patients to normal levels, and it appears likely that their primary usefulness will be in preventive maintenance. Bisphosphonates may be useful agents for managing established osteoporosis, but the restoration of lost bone remains elusive. Dramatic gains in bone mass can be achieved with sodium fluoride, but serious questions concerning bone quality and drug toxicity limit the clinical use of this agent. Modern technology offers the hope that further progress may come about through the development of growth factors and other osteotropic compounds for clinical use.

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Painful Subacute Thyroiditis in Hawaii

ROBERT A. NORDYKE, MD; FRED I. GILBERT, Jr, MD; *and* CHRIS LEW, MD, *Honolulu, Hawaii*

Between 1960 and 1982 we prospectively studied 269 patients with painful subacute thyroiditis to determine the demographic characteristics, seasonality, and natural course of the disease. The mean age for all patients was 37.1 years. The female:male ratio was 6.7:1. At the first visit, disease was bilateral in 69%. No epidemic or seasonal pattern was identified. The mean duration of thyroid tenderness was 2.2 months and that of palpable thyroid lumps was 2.8 months. This time difference, sometimes lasting many months, left a painfree "window" during which the palpable hard residual mass of subacute thyroiditis may be confused with other thyroid problems, especially cancer.

(Nordyke RA, Gilbert FI Jr, Lew C: Painful subacute thyroiditis in Hawaii. West J Med 1991 Jul; 155:61-63)

Subacute (de Quervain's) thyroiditis is an inflammatory condition of the thyroid probably caused by a virus, with a possible genetic predisposition.[1,2] It can be localized or generalized, mild or severe, lasting weeks to many months. At different stages it may be confused with a "sore throat," the hyperthyroidism of Graves' disease, thyroid cancer, or bleeding into a cyst. Various authors report a female:male ratio of 3:1 to 7:1 and a peak incidence between 40 and 50 years of age.[3-6] Based on the number of patients seen at major hospitals, the incidence of the disease has been hypothesized to be higher on the West Coast of the United States compared to the East,[7,8] but this has been questioned.[9] The incidence appears to be highly variable worldwide.[8,10,11] Some studies have reported a significant increase during the summer months,[3,4,12] and others have found no seasonal trend.[6,9] Excellent general reviews of subacute thyroiditis are available.[1,11]

We examined the demographic characteristics (age, sex, and race) and the seasonal occurrence of disease of 269 patients with painful subacute thyroiditis seen at Straub Clinic in Hawaii. In addition, the clinical course of 70 patients was studied with special attention to the painfree "window"—the time between the cessation of tenderness and the disappearance of palpable thyroid abnormalities attributable to thyroiditis. Patients seen for the first time during this window are likely to be misdiagnosed because tenderness is absent and the gland often feels unusually hard and irregular.

Patients and Methods

Study Population

This study included all patients referred to the thyroid clinic of Straub Clinic in Honolulu between 1960 and 1982 who were diagnosed with painful subacute thyroiditis. Some patients were referred by outer-island physicians, but most were sent to us by Straub Clinic physicians (ranging from 36 in 1960 to 105 in 1982). During that time, Straub was entirely a fee-for-service facility, caring for about 15% of the civilian population of the island of Oahu.

All patients had thyroid gland tenderness at their first visit or by recent history (we excluded patients falling into the more recently described nontender variants[11,12]). There were 269 such cases. Of these, 70 were observed through the course of their disease.

Patient Examination

Clinical examination was similar in all patients, using a standardized work sheet[13] that contained the referral source, reason for the referral, demographic information (age, sex, and race), chief complaint, present illness, history of thyroid disease, physical findings related to the thyroid, clinical impression, and final diagnosis after all data became available. The diagnosis was made on the basis of typical signs and symptoms, including tenderness corresponding to a palpable mass, with pain often radiating to the ipsilateral jaw and ear, and clinical follow-up. When needed for confirmation, laboratory tests were obtained, including serum thyroxine estimates, iodine 131 thyroidal uptake at 6 or 24 hours, erythrocyte sedimentation rate, and thyroid scan. On the first visit, special attention was given to the time symptoms began, severity of symptoms, the initial location of pain and tenderness, thyroid gland size and palpation characteristics, and anatomic areas of tenderness and enlargement (localized, unilateral nonlocalized, or bilateral). On follow-up visits, special attention was given to gland size, palpable enlargements, tenderness, the correspondence of enlargements and tenderness, the migration of findings, and the time of the disappearance of tenderness and palpable abnormalities.

Results

Demographic Characteristics

Among the 269 patients, 47% were white, 24% Japanese, and the rest were various other races. The white:Japanese ratio was 2:1. This ratio is 1.8:1 for all of Straub Clinic's patients. The mean age was 37.1 years with a range from 4 to 86. Most cases (77%) occurred between ages 20 and 49 (Figure 1). The age distribution for male and female patients was similar. Female cases predominated at all ages, accounting for 87% of the 269 cases and giving a female:male ratio of 6.7:1. Among the 70 patients observed through the course of their illness, women predominated by a ratio of 6.1:1; 46%

From the Department of Nuclear Medicine, Straub Clinic & Hospital (Drs Nordyke and Gilbert), and the Department of Medicine, University of Hawaii John A. Burns School of Medicine (Drs Nordyke, Gilbert, and Lew), Honolulu, Hawaii.

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Reprint requests to Robert A. Nordyke, MD, Straub Clinic & Hospital, 888 S King St, Honolulu, HI 96813.

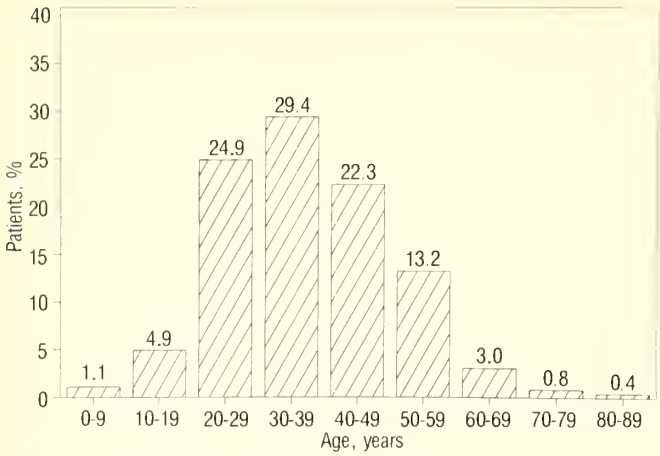

Figure 1.—The graph depicts the age distribution by decade of 269 patients with painful subacute thyroiditis.

were white and 27% were Japanese. The mean age for female patients was 41.1 years with a range of 11 to 80.

Seasonal Variation

The distribution of cases diagnosed in each month throughout the year is presented in Figure 2. There was no summer peak, in contrast to the findings of some reports.[3,4,12] The only apparent trend, a lower percentage of cases in April through August compared with September through March, was not statistically significant. The one exception to this trend was the low incidence in December.

Localization Within the Thyroid Gland

When cases were categorized by area of the gland involved on the first visit, the area was discretely localized in 16%, nonlocalized but unilateral in 15%, and bilateral—usually diffuse, and including those that had migrated by the time of the first observation—in 69%. All three categories of involvement were more common in white patients than in Japanese.

Duration of Tenderness and Palpable Lumps

The progress of tenderness and palpable lumps was observed for 70 patients throughout the course of their disease. The time symptoms began was estimated by history obtained at the first visit. Tenderness and palpable lumps disappeared at about the same time in 50 patients (72%), and in the other 20 patients (28%) tenderness ceased first, leaving areas of firm or hard lumps that disappeared later. The duration of tenderness for the entire group was 65.4 ± 42.5 days (mean ± standard deviation). The duration of palpable abnormalities that later disappeared spontaneously was 83.5 ± 51.5 days. Two patients had prolonged, severe, debilitating pain and tenderness poorly responsive to treatment with prednisone. One had a near-total thyroidectomy and the other an ablative dose of sodium iodide I 131. Both became free of pain and tenderness after their definitive treatment.

The percentages of patients with pain and palpable abnormalities at various times after the disease occurred are given in Figure 3, which illustrates the magnitude of the painfree window. More patients continued to have palpable abnormalities than persistent pain at any given duration of follow-up. The figure also shows the broad range of durations of pain and palpable lumps. Some patients were symptomfree within a week or two; for others, pain and palpable irregularities persisted for months.

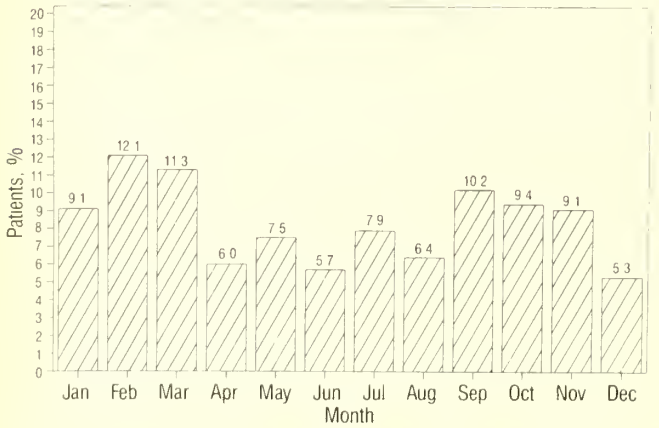

Figure 2.—The seasonal distribution of all 269 patients is shown. The incidence is slightly less in April through August and in December, but these variations are not statistically significant.

Discussion

The diagnosis of painful subacute thyroiditis can usually be made on clinical grounds alone. In nearly all instances, its course is benign and self-limited, leaving no functional or anatomic residuals. In the more severe and diffuse cases, temporary hyperthyroidism is common, and in those same cases temporary subclinical hypothyroidism often occurs.[1,5,14] The rare reported instances of permanent clinical hypothyroidism usually have causes other than subacute thyroiditis, such as a previous subtotal thyroidectomy or Hashimoto's thyroiditis.[14,15] We have found many patients with temporary hyperthyroidism but none with permanent hypothyroidism. We have not carried out long-term follow-up studies on our patients, however.

In this study we reviewed the first-visit characteristics of 269 patients with painful subacute thyroiditis. Of these patients, 90% were aged 20 to 59 years, with comparable age patterns for male and female patients. The mean age of our patients was 37.1 years; the mean age in most other reports has been at least 40.[4-6,9,12] For the entire series, there was a preponderance of female to male patients (6.7:1), slightly higher than in most reports in the literature. The distribution

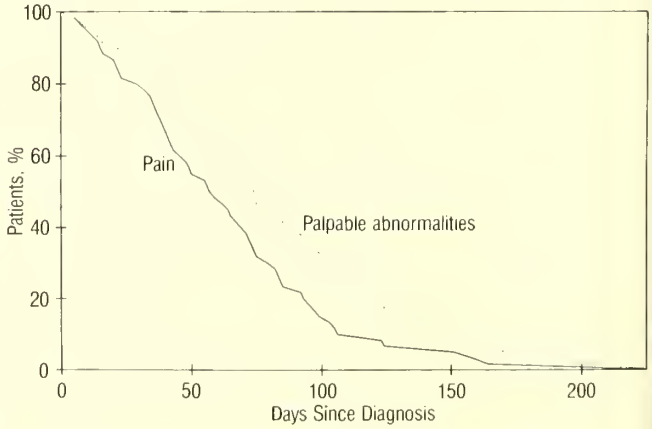

Figure 3.—The graph correlates the time from the beginning of pain to the disappearance of pain and palpable abnormalities in 70 patients observed through the course of the disease. In all instances, pain and tenderness ceased first. The mean duration of pain was 65 days versus 84 days for palpable abnormalities.

of whites, Japanese, and other races reflected that expected at the Straub Clinic.

In about two thirds of the patients, the distribution was bilateral and in a third it was unilateral, either diffuse or localized. This anatomic distribution is similar to observations from other areas.[5,16,17]

Our seasonal trends differ from some previous reports. Three studies found more cases diagnosed in summer than during other seasons. The peak months were July and August in Italy,[4] June through August in Japan,[3] and December through May in Australia.[12] The concurrence of subacute thyroiditis and viral activity, particularly enteroviruses, was discussed by these investigators. By contrast, a study from Minnesota[9] found no seasonal trends or relationship with enteroviruses. The study was population based rather than a review of clinical cases, as in the other reports. Similarly, a study from Finland[6] found no seasonal differences. Our cases clearly did not cluster in the summer months. Our peak incidence period included January through March, three of the coolest months in Hawaii. The percentage of cases dropped beginning in April, when temperatures become warmer, and remained low through August, one of the hottest months. The available studies do not indicate a consistent seasonal pattern across different geographic regions.

Because treatment is limited to pain relief and justifiable reassurance, it is important to provide a reasonable estimate of the duration of the signs and symptoms a patient will experience. The results of our study of 70 patients observed through the course of the disease answer some of the patient's concerns. The mean duration of pain was 2.2 months, and the mean duration of palpable abnormalities was 2.8 months. For a few patients lumps or irregularities persisted for many weeks after pain and tenderness were gone.

Painful subacute thyroiditis in Hawaii appears to be similar to the disease in other areas. It is much more common in women, and most cases appeared in patients aged 20 through 60 years. The disease is likely to start in both lobes or to extend later to the opposite lobe rather than to remain unilateral. Noteworthy in our study was the delay between the disappearance of pain and tenderness and the regression of palpable lumps. It is during this window, which may last many months, that diagnostic difficulty can arise. The firm or hard lumps are easily confused with cancer,[10] and unnecessary surgical therapy has been reported.[1,15,18] For this reason, the diagnosis of subacute thyroiditis should be considered for patients presenting with firm or hard lumps or irregularities of the thyroid gland despite the absence of tenderness. A careful history of pain and tenderness will usually point to the correct diagnosis. If such a history is not obtained or clinical findings are suspicious for thyroid neoplasm, consideration should be given to obtaining a cytologic diagnosis with a fine-needle aspiration biopsy.

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Epitomes

Important Advances in Clinical Medicine

Neurology

The Scientific Board of the California Medical Association presents the following inventory of items of progress in neurology. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome, and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, researchers, or scholars to stay abreast of these items of progress in neurology that have recently achieved a substantial degree of authoritative acceptance, whether in their own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Neurology of the California Medical Association, and the summaries were prepared under its direction.

Reprint requests to Division of Scientific and Educational Activities,
California Medical Association, PO Box 7690, San Francisco, CA 94120-7690

Use of Antiepileptic Drugs in Pregnancy

THE TREATMENT OF epileptic women of childbearing age is highly controversial. All antiepileptic drugs have the potential for causing birth defects, although genetics and socioeconomic status play roles as well. These birth defects may be caused by direct drug effect, drug interactions, drug metabolites (epoxides), or folate deficiency caused by certain antiepileptic drugs. Congenital malformations (defined as requiring medical or surgical intervention) such as spina bifida, cleft lip-palate, and congenital heart defects are the main concerns when using these drugs. These defects occur in approximately 7.3% of children of epileptic mothers—more than double that for infants not having exposure to the drugs. It is now known that the risk of birth defects increases with the use of multiple drugs and higher drug levels.

Trimethadione, although now rarely used, causes a 50% rate of birth defects and is absolutely contraindicated for use in pregnancy. Taking valproic acid causes a 1.5% to 2% risk of spina bifida, 20 times higher than in the general population. Carbamazepine therapy has also been found to cause a 0.5% to 1% risk of spina bifida.

In the past, certain drugs were thought to cause specific congenital anomalies, such as the "fetal hydantoin syndrome." Researchers now prefer the term "fetal anticonvulsant syndrome" because all drugs used to treat epilepsy in women may produce dysmorphic features in their children. It should be noted that dysmorphic features were noted in the offspring of epileptic women before the use of anticonvulsant drugs. The significance of these anomalies is unclear, and research is underway to determine the cause of minor anomalies.

Prenatal counseling is the most important aspect in the treatment of epileptic women of childbearing age because the teratogenic effects occur during the first trimester. Women should be cautioned regarding the risks of congenital malformations and of the risks of seizures for themselves and their unborn children should they decide to discontinue their medication. Although rare, there have been reports of fetal death after a generalized tonic-clonic seizure. While it might seem reasonable to discontinue all antiepileptic drugs before conception, this is not wise because a third of all women experience an increased rate of seizures during pregnancy. The mechanism of this increase is not clear but is not necessarily related to falling drug levels. A decrease of serum anticonvulsant levels in itself does not justify an increased dosage. For example, total concentrations of phenytoin and valproic acid may fall, but free levels—which should be monitored monthly—may remain stable. Patients should be seen frequently during pregnancy and their drug levels monitored regularly. Pregnant women who have seizures have an increased risk for toxemia.

Certain steps can be taken before conception to minimize the risk of malformations. Because there is an increased risk of birth defects with the use of multiple drugs and higher drug levels, a switch to single-drug therapy, if possible, should be made, and the lowest effective dose should be used. Multivitamins and folic acid should be given because birth defects may be caused by folate deficiency. If valproic acid, carbamazepine, or both are used, abdominal ultrasonography should be done and α-fetoprotein levels in the amniotic fluid should be measured. Finally, phytonadione vitamin K_1 therapy, 20 mg per day, should be begun during the last four weeks of pregnancy to prevent neonatal hemorrhage.

Although all antiepileptic drugs except valproic acid are present in breast milk, few problems are linked to breast-feeding. Breast-feeding should be discontinued if sedation is noted in the infant, however. If breast-feeding is discontinued, drug withdrawal may occur in the infant.

Although the risk of congenital malformations in children of epileptic women using antiepileptic drugs is twice that of the general population, epileptic women should be informed that the overall outcome is usually good and that more than 90% have normal children.

MARIAN V. SOWA, MD
Long Beach, California

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Human T-cell Leukemia Virus Myelopathy

HUMAN T-CELL LEUKEMIA VIRUS (HTLV-1), the first human retrovirus discovered, was found in association with adult T-cell leukemia or lymphoma in 1980. Since then, this virus has been recognized as the probable cause of some cases of tropical spastic paraplegia and the closely related, if not identical, HTLV-1–associated myelopathy in southern Japan. Both of these conditions are characterized by slowly progressive paraparesis in adults, with variable sensory manifestations, usually without remission. Because these disorders are endemic to parts of the Caribbean and to southern Japan, most of the described cases have occurred in black or Japanese patients.

The virus is transmittable by breast-feeding; the substitution of bottle feeding prevents vertical transmission. The virus is also possibly transmitted by sexual contact, shared needles, and blood transfusion. In a methadone maintenance clinic in New Orleans, Louisiana, 49% of patients were HTLV-1–positive; 5% to 14% of patients attending a sexually transmitted diseases clinic in Jamaica were HTLV-1–positive; the percentage increased with age. Cases of myelopathy due to transfusion-transmitted virus have been reported.

Recent epidemiologic studies indicate that HTLV-1 is also present in temperate climates. In the United States, the highest frequency of HTLV-1 antibody–positive persons is found in the Southeast among intravenous drug users and prostitutes. The virus is also present in the blood supply: the risk of receiving HTLV-1 by transfusion was 0.024% per unit in one US study.

Most people infected with HTLV-1 are asymptomatic. There may be a latent period of years between infection and the occurrence of clinical symptoms. The natural history of the infection and the factors influencing disease production and expression are poorly understood. Host immune responses may help determine the occurrence of inflammatory myelopathy in some infected persons but not others.

When the diagnosis of HTLV-1 myelopathy is suspected, serum and cerebrospinal fluid (CSF) specimens should be sent for HTLV-1 antibody determinations. The screening tests are done on all donor blood specimens and thus should be available in most communities. The screening test is an enzyme-linked immunosorbent assay. The test is sensitive and false-positives occur, so positive tests should be confirmed by a Western blot assay in which antibodies to various specific antigens of the HTLV-1 virus are determined.

Some findings in patients with tropical spastic paresis or HTLV-1–associated myelopathy are similar to those in multiple sclerosis: scattered white matter lesions with increased T2 signal on head magnetic resonance imaging, delayed evoked responses, and a mild pleocytosis on CSF examination, with an increase in immunoglobulin (Ig) G levels in the CSF and oligoclonal bands. Important differences are the epidemiologic pattern, the paucity of remissions, the pathologic picture, and positive HTLV-1 antibody tests in serum and CSF in patients with tropical spastic paraparesis or HTLV-1–associated myelopathy. The disorder is generally more inflammatory than seen in the usual case of multiple sclerosis; the typical plaque of multiple sclerosis has not been seen. In tropical spastic paraparesis, the virus is found in the cells in the CSF, and the increased CSF IgG is largely directed against HTLV-1.

A few early reports suggested that HTLV-1 antibody and antigen could be detected in serum and CSF in some patients with multiple sclerosis, but a large number of subsequent studies have had negative results. There is a consensus that HTLV-1 is not the cause of multiple sclerosis, but some speculate that a related and as-yet-unidentified retrovirus could be responsible.

Another syndrome associated with HTLV-1 infection is sporadic familial spastic paraplegia, a possible result of the vertical transmission of the virus through breast-feeding. Infection with HTLV-1 can also cause a fatal subacute meningoencephalitis. Reports of associations with other neurologic syndromes must be viewed cautiously, especially from endemic areas. The presence of pleocytosis and a local synthesis of IgG directed against HTLV-1, however, are presumptive evidence of a causal connection.

WILLIAM A. SIBLEY, MD
Tucson, Arizona

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Acquired Immunodeficiency Syndrome Dementia

ACQUIRED IMMUNODEFICIENCY SYNDROME (AIDS) dementia complex, also called AIDS encephalopathy, is the most frequent neurologic complication of AIDS. It affects 40% to 60% of patients, most commonly those with advanced immunosuppression.

The complex is characterized by a slowing of cognitive and motor abilities. Early in the course, patients show difficulties with concentration and memory, as well as apathy and social withdrawal that may be mistaken for depression. Hyperreflexia, a slowing of the rapid movements of eyes and limbs, and pathologic reflexes are commonly found on neurologic examination. Psychiatric symptoms may be prominent, and psychosis or mania may be the presenting manifestation. As the disease progresses, intellectual function continues to decline, and, although alert, patients eventually become mute, paraparetic, and incontinent. Treatment with zidovudine may result in improvement.

Cranial computed tomographic (CT) scans show increased ventricular and sulcal size, consistent with cerebral atrophy. Although CT sometimes shows white matter changes, magnetic resonance images of brain frequently show diffuse or patchy increased signals in the white matter, especially on T2-weighted images. Cerebrospinal fluid (CSF) findings in AIDS dementia complex are similar to those seen in persons infected with the human immunodeficiency virus type I (HIV-1) without dementia and include elevated protein levels, oligoclonal bands, intrathecal synthesis of anti–HIV-1 antibodies, and virus isolation by culture. Cerebrospinal fluid levels of HIV-1 core antigen (p24), β_2-microglobulin, and neopterin seem to correlate with the severity of dementia. The main practical value of neuroimaging and CSF examination is in excluding other opportunistic disorders that may mimic AIDS dementia complex or exist concomitantly. Neuropsychological test results show impairment in motor speed and fine control, concentration,

problem solving, and visuospatial performance. The complex remains a clinical diagnosis; neuroimaging studies, CSF examination, and neuropsychological test results support but do not establish the diagnosis.

The mechanism by which HIV-1 infection causes dementia is unclear because in brain most virus is found in macrophages and microglia, not in neurons. The HIV-1 envelope protein, gp120, can kill rodent neurons in vitro, perhaps by interfering with the neurotropic effects of vasoactive intestinal peptide, by increasing intracellular calcium concentrations, or by both mechanisms. Also, HIV-1–infected mononuclear cells release neurotoxins that kill chick and rat neurons in culture by binding to *N*-methyl-D-aspartate receptors. These data raise the possibility of specific treatments for AIDS dementia complex, such as calcium channel blockers or *N*-methyl-D-aspartate receptor antagonists.

CHRISTINA MARRA, MD
Seattle, Washington

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Treatment of Cluster Headaches

CLUSTER HEADACHE is an excruciating unilateral headache often mistaken for migraine. Recent evidence suggests different biochemical and physiologic mechanisms for each headache type. Failure to make this distinction can result in ineffectual treatment and frustration for clinicians and patients.

Cluster headache has a male to female ratio of approximately 6:1. The age of first occurrence ranges from 20 to 50 years, with a peak of between 21 and 30 years. Attacks are paroxysmal, unilateral, stabbing or piercing—rather than throbbing, as with migraines—and are usually associated with nasal stuffiness, tearing, and conjunctival hyperemia. There is no aura or throbbing sensation as with migraine. Attacks last about 45 minutes and may occur several times during the day, frequently occurring at the same time each day, often between 9 PM and 10 AM, and most often during rapid-eye-movement (REM) sleep. Headaches occur in cycles lasting from four to eight weeks, followed by a headache-free interval of several weeks to months. Subclassifications include episodic, chronic, subchronic, and a variant called chronic paroxysmal hemicrania.

Physiologic abnormalities may include a disturbance in lower brain-stem mechanisms as reflected in prolonged brain-stem auditory evoked potentials with particular prolongation of latencies I to III. Unilateral disturbances in central autonomic vasomotor function have also been found. Disturbances in histamine and serotonin sensitivity have been described, as have disturbances in REM sleep patterns, though the exact pathogenic pathways have not been established. A "trigeminovascular" pathway giving rise to cerebral hypofusion has been proposed.

Treatment is divided into symptomatic and prophylactic therapies, with variations according to headache subtype and patient compliance. For episodic cluster headaches, inhaled agents are most effective because of their rapid absorption. Ergotamine aerosol, taken one to three inhalations at the start of a headache, has been effective as much as 80% of the time provided the inhaler is shaken vigorously before use and the patient inhales each dose after a forced exhalation. Inhaling 100% oxygen through a tight mask at 7 to 10 liters per minute for 15 minutes has also been highly effective; it can be used as much as five times per day. Administering 1 ml of a 4% topical lidocaine solution intranasally ipsilateral to the headache has been effective, but it may be difficult for patients to self-administer in the throes of an acute attack. Dihydroergotamine mesylate, 1 to 2 mg given intravenously, has been reported effective if administered within the first few minutes of an attack; the parenteral or subcutaneous routes have been less successful.

The most effective prophylaxis for episodic cluster is the use of ergotamine preparations, as ergotamine tartrate, 1 to 2 mg two to three times a day taken orally, or, for nocturnal headache, 2 mg at bedtime. Methysergide maleate in a dose of 2 mg given three to four times a day, often combined with cyproheptadine, 8 mg taken at bedtime, is also useful. Calcium channel blockers, particularly verapamil, have been highly effective in episodic cluster prophylaxis, provided the cardiac and side effects of the drug can be tolerated. Alternative regimens include verapamil, 80 mg three to four times a day or 180 to 240 mg in the sustained-release form given daily; nimodipine, as much as 240 mg per day; or nifedipine, with doses ranging between 40 and 120 mg per day. Steroids given for one to two weeks can be effective used either alone or in conjunction with ergotamine preparations. The use of dexamethasone, 4 mg twice a day for two weeks, then four times a day for a week, has been recommended; it is thought to work by inhibiting histamine decarboxylases, mast cell degranulation, and histamine release. Prednisone given in large initial doses tapered over one to two weeks with subsequent alternate-day therapy has been reported as useful, though dosage schedules vary widely, with the initial doses being between 40 and 80 mg.

For patients whose headaches are refractory to the above therapies, lithium taken in daily doses ranging from 300 to 1,500 mg—with the usual range being 600 to 900 mg—titrated to the therapeutic range has been reported effective in as much as 80% of patients, although the panoply of side effects often defeats patient acceptance. A lithium citrate solution dissolved in fruit juice may reduce gastrointestinal symptoms.

Patients with constant, or chronic, cluster headaches are more difficult to treat and have been reported to have elevated scores on the Minnesota Multiphasic Personality Inventory for depression, hysteria, and addiction tendencies. Combined regimens of calcium channel blockers and ergotamine with the addition of lithium in the schedules mentioned have been advocated with varying degrees of success.

A subclass or variant, chronic paroxysmal hemicrania, has been described as similar to cluster headache but with increased frequency, shorter duration, less restlessness, and, at times, provocation of the attack by neck flexion. Unlike cluster headache, chronic paroxysmal hemicrania is said to be totally responsive to the use of indomethacin given in divided doses from 70 to 100 mg per day when tolerated.

Patients should be warned that any alcohol or tobacco use may incite attacks, though typically they will have discovered this before consulting a physician. The use of narcotic analgesics is discouraged in all but the most intractable cases and only then when given under careful supervision in a

controlled hospital setting, usually to wean patients off analgesics injudiciously prescribed elsewhere. The use of narcotic analgesics is contraindicated in patients with chronic cluster headache or chronic paroxysmal hemicrania.

In all cases, patients should be reassured of the usually self-limiting nature of their attacks and that effective medications and treatments are available to relieve their suffering. Family, friends, and co-workers should be informed of the nature and pattern of cluster headaches so that they, with the physician, can support the patient with understanding and compassion.

DAVID C. AGNEW, MD
Santa Barbara, California

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Electroencephalographic Brain Mapping

ELECTROENCEPHALOGRAPHIC (EEG) brain mapping is a digital technique that generates color-coded topographic maps of EEG activity as measured on the scalp. Such maps can help localize EEG activity such as regional slowing. Maps have also been applied to evoked potentials, localizing peaks. Statistical techniques can score how closely an individual patient's brain electrical activity corresponds to similar features in a normal population.

Electroencephalograms and evoked potentials are entered into a small computer, which calculates the amount of EEG activity in several frequency bands or the amplitudes of evoked potential peaks. The operator can print colored displays of scalp electrical activity that are abnormal or interesting. These topographic color-coded displays can then be used to communicate the location of abnormalities to patients or to physicians who are unfamiliar with reading routine polygraph EEG and evoked potential displays.

The techniques are subject to several kinds of problems. Some technical artifacts are difficult to screen out, misleading the computer into considering these to be abnormal EEG features. These include common EEG artifacts as well as new problems introduced by the computer processing itself. Clinical issues may confound attempts at automated computer diagnosis of abnormalities, including the effects of medication and a variety of medical conditions. Many different types of EEG brain mapping equipment are on the market, and applications based on one type of machine or technique are not necessarily usable with other kinds of machines. Statistical problems have also arisen. For example, basic statistical assumptions are not necessarily met in this EEG application. Confusion also exists between statistical significance and the implications of disease. Because of the variety of problems, EEG brain map tests are considered controversial for use in clinical settings and are not yet widely used or accepted.

These techniques have been applied to a variety of neurologic and psychiatric disorders. In cerebrovascular disease, these techniques can help to localize regions of impairment and detect some subtle electrical abnormalities that might be overlooked on routine EEG reading. In epilepsy, the use of coherence can help to separate subtypes of bifrontal spike-wave activity, differentiating primary generalized from focal disease with secondary bilateral synchrony. In dementia, the techniques can help to decide that EEG or evoked potential results are abnormal, especially for records in which the degree of abnormality is mild or subtle.

Insufficient medical literature is available to judge whether these techniques have any merit in the differential diagnosis of types of depression, schizophrenia, dyslexia, and neurobehavioral syndromes resulting from head trauma.

Electroencephalographic brain mapping makes the recording or reading of an EEG test more difficult. Technologists and physicians using these techniques need to be familiar with and competent in routine EEG and to have additional skills, knowledge, and abilities in the computerized techniques. Records need to be run carefully and interpreted cautiously because these computer-based techniques are prone to giving a false impression of "abnormality." Certain kinds of EEG abnormalities can be overlooked, such as epileptic spikes or other intermittent features. Physicians interpreting the EEG brain map test must be competent at reading routine EEG records. A simultaneous traditional polygraph EEG is considered a necessary part of any EEG brain map test, and the computer-based results should be considered only adjuncts to interpreting the standard EEG.

MARC R. NUWER, MD, PhD
Los Angeles, California

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Transcranial Doppler Study

TRANSCRANIAL DOPPLER is a noninvasive ultrasound technique that measures intracranial blood flow. It uses a pulsed-wave Doppler signal of low frequency (2 MHz) that can detect blood flow around the circle of Willis and in the vertebral-basilar arteries. Calculations of peak systolic and diastolic velocities and averaged flow (mean envelope) quantify blood flow. The accuracy of the results depends on the skill and experience of the operator and a number of biologic variables such as age, blood pressure, hematocrit, and medications that the patient may be taking.

In acute situations, the transcranial Doppler technique can measure the presence and degree of vasospasm from subarachnoid hemorrhage. The early detection of increased flow velocities can indicate the need for calcium channel blocking agents or hypervolemic-hypertensive techniques. The flow from arteriovenous malformations can be monitored preoperatively and postoperatively. These techniques are used in conjunction with anatomic techniques such as magnetic resonance imaging and angiography. Transcranial Doppler examination has also been used in the operating room to monitor cranial blood flow during carotid endarterectomies and cardiac bypass procedures. Blood flow tends

to decrease as intracranial pressure increases, and the procedure assists in the monitoring of intracranial pressure changes. More recently, transcranial Doppler has been used in the evaluation of brain death with the observation of a pattern of "to-and-fro" flow in near-dead or brain-dead patients.

The procedure has been used to evaluate cerebrovascular disease in ambulatory patients. Altered intracranial perfusion from extracranial carotid occlusive disease and primary intracranial vascular disorders can be detected. Carbon dioxide challenge techniques can influence blood vessel autoregulation in cerebral arteries and are used in conjunction with carotid compression techniques to determine the extent of carotid vascular disease that is present and to detect compensatory collateral blood flow across the circle of Willis in affected areas. The studies are used in association with other techniques, including duplex extracranial evaluations, angiography, and magnetic resonance imaging. Research studies are being undertaken to evaluate common conditions such as migraine, dizziness, syncope, and measures of autonomic regulation. The technique holds promise for the objective evaluations of many of these conditions.

Transcranial Doppler examination is a safe, useful technique that allows a quick screening of the cerebral circulation in a number of clinical situations. As more widespread application becomes available, its specific uses will be clarified.

KENNETH L. NUDLEMAN, MD
Orange, California

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Myth of the Chronic Fatigue Syndrome

THE CHRONIC FATIGUE SYNDROME is a symptom complex characterized by fatigue, myalgias, arthralgias, neurologic symptoms—headaches, paresthesias, dizziness—lymph node swelling or tenderness, cognitive dysfunction, sleep disorders, and depression. The symptoms are similar to those seen in inflammatory illnesses and can be induced by the systemic administration of interferon beta. Severe fatigue is a perplexing and constant complaint in many patients with multiple sclerosis. This indicates that the perception of energy level has a sensitive physiologic basis that is dependent on the homeostasis of other body systems.

The chronic fatigue syndrome has gained popularity among the lay public and has stimulated considerable scientific debate about its existence. Many investigators and practitioners have attributed the disorder to chronic depression. Difficulty arises from the diverse symptoms associated with fatigue states; fatigue is a prominent feature of many systemic, neurologic, and psychiatric disorders. Also, fatigue is a subjective complaint without a quantifiable measure. This interweaving of many symptoms and diagnoses with disabling fatigue makes it difficult to compare patient groups. Terms applied to disorders that probably represent chronic fatigue syndrome are chronic infectious mononucleosis, myalgic encephalomyelitis, idiopathic chronic fatigue and myalgia syndrome, epidemic neuromyasthenia, postviral fatigue syndrome, and fibrositis-fibromyalgia.

The Centers for Disease Control (CDC) made a major advance by recommending a working case definition: the diagnosis of chronic fatigue syndrome is restricted to patients with fatigue that occurs abruptly, is present for more than six months, and prevents the patient from performing usual activities 50% of the time. In addition, there is no identifiable systemic, neurologic, or psychiatric illness that could otherwise explain the symptom complex. The patient should have a minimum of 6 of 11 symptoms (mild fever, sore throat, painful lymph nodes, diffuse muscle weakness, myalgia, postexercise fatigue, headaches, migratory arthralgia, neuropsychological complaints, sleep disturbance, abrupt onset of complaints) and 2 of 3 physical signs (slightly elevated temperature, nonexudative pharyngitis, palpable or tender lymph nodes). The CDC's recommendations consolidate the syndrome definition, allowing for a large number of patients to be identified and enrolled into research protocols.

Current research on the chronic fatigue syndrome has focused on treatment, physiologic mechanisms, clinical subtypes, fatigue quantification measures and markers, and the association with chronic infections. Although several potential infectious agents have been identified, including Epstein-Barr virus, retroviruses (possibly human T-cell lymphotropic virus type II), human herpesvirus type 6, and coxsackieviruses, none has emerged as an indisputable cause of the syndrome. Research has also focused on identifying a metabolic marker using phosphate 31 magnetic resonance spectroscopy and a physiologic marker using single-fiber electromyography of muscle fatigue. Results have been mixed, and further efforts to delineate their role in evaluating the syndrome will be necessary. The question of whether fatigue is mediated by central nervous system or peripheral mechanisms has considerable scientific and therapeutic implications. Treatment remains focused on symptom and supportive management as no antiviral agent has proved successful. The answers to the many issues inherent in the chronic fatigue syndrome await the results of research.

RONALD S. MURRAY, MD
Englewood, Colorado

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Selegiline (Eldepryl) for Parkinson's Disease

PARKINSON'S DISEASE has attracted attention recently as concepts of cause and treatment change and our population ages. An important advance in treatment is the use of selegiline hydrochloride (Deprenyl [Eldepryl]) for prophylaxis and the relief of symptoms. Selegiline was released in 1989 as an adjunct to levodopa for the treatment of Parkinson's disease. Since then, exciting new information about an alternative application has become available.

Two observations prompted the use of the type B monoamine oxidase inhibitor selegiline as a prophylactic agent for Parkinson's disease. Administering 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP, a neurotoxin) can produce parkinsonism in humans and primates. It was discovered that this could be prevented in primates by pretreatment with selegiline. Investigators have hypothesized that the breakdown of dopamine itself (partially through monoamine

oxidase B) could produce damage to the degenerating nigrostriatal neurons involved in Parkinson's disease. With this information, a large multicenter trial was undertaken comparing the use of an inhibitor of monoamine oxidase B (selegiline) or placebo in the early stages of the disease. The end point was the need for levodopa treatment, indicating a progression of illness. Investigators thought that the use of selegiline slowed the progression of the Parkinson's disease. Critics feel that selegiline is simply a mild antiparkinson medication. This issue should be addressed in future studies, but because selegiline may offer a protective effect and delay the need for levodopa therapy, a regimen of this medication should be started in newly diagnosed patients.

Besides its use as a protective agent early in the disease, selegiline is recognized as an adjunct to levodopa therapy in patients with more advanced disease. It can prolong the effect of levodopa in patients experiencing "wearing-off phenomenon," in which the duration of the effect of levodopa is reduced. Its use is not helpful in patients with the rapidly fluctuating "on-off phenomenon" and may worsen dyskinesias. The dose in both prophylactic and symptomatic therapies is 5 mg by mouth in the morning and at noon. Lower doses may be effective in some patients at a considerably reduced cost. Because of a mild amphetamine effect, the medication should not be given after noon. Side effects are minimal when used alone but greater when combined with levodopa and include nausea, postural hypotension, confusion, and dyskinesias. By starting with half a tablet once a day and slowly increasing the dose as the patient tolerates, it may be possible to establish a dose at which the patient obtains benefit (prolonged levodopa effect) with few side effects. Lowering the dose of levodopa may reduce the side effects of the combination, but it usually also lessens efficacy.

CHERYL H. WATERS, MD, FRCPC
Los Angeles, California

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Intravenous γ-Globulin for Chronic Inflammatory Demyelinating Polyneuropathy and Myasthenia Gravis

IMMUNE GLOBULIN PREPARATIONS extracted from human blood until recently had to be given intramuscularly. Now, preparations of human immune globulin are available that can be infused intravenously safely over several hours. These preparations, purified by cold liquid ethanol fractionation of large pools of human plasma, have not transmitted non-A, non-B hepatitis, human immunodeficiency virus infection, or the acquired immunodeficiency syndrome. Anaphylaxis to intravenous immune globulin can develop, however, in persons with immunoglobulin (Ig) A deficiency, who often have IgG antibodies to IgA.

Intravenous immune globulin has been found useful in the treatment of primary immunodeficiency syndromes, neonatal infections, bone marrow transplantation, chronic lymphocytic leukemia, idiopathic thrombocytopenic purpura, and Kawasaki syndrome. The minimal effective dose in most of these studies is 150 mg per kg of body weight, and many clinicians feel that higher doses up to 1 gram • kg^{-1} • day^{-1} confer superior results.

Dramatic responses to the use of intravenous immune globulin of intractable or progressive chronic inflammatory demyelinating neuropathy have occurred within days of starting treatment at a dose of 400 mg • kg^{-1} • day^{-1} for three to five days. A slow rate of infusion, between 40 and 100 ml per hour, of a 5% to 6% solution is recommended to minimize adverse reactions of headache, myalgia, fever, chills, lightheadedness, nausea, or edema. Clinical improvement lasts for months in some cases, while other patients begin to relapse four to six weeks after treatment and may require regular prophylactic outpatient infusions at doses of 150 to 300 mg per kg every one or two weeks. The successful use of intravenous immune globulin in children with acute inflammatory demyelinating neuropathy (or Guillain-Barré syndrome) has recently been reported in abstract form.

Preliminary but favorable results have also been reported for intravenous immune globulin treatment of intractable myasthenia gravis at doses of 0.4 to 1.0 grams • kg^{-1} • day^{-1} for five days. Clinical improvement can begin within nine days of starting treatment and last as long as three months, although a second course of intravenous immune globulin may be required because of relapse. A disturbing aspect of intravenous immune globulin treatment of myasthenia gravis is the life-threatening exacerbation that occurs in some patients early in the course of treatment.

In the United States, intravenous immune globulin treatment for a 70-kg person costs more than $1,000 per day, which is perhaps no more expensive than plasma exchange, and it is apparently safer than long-term prednisone or immunosuppressive therapy. The efficacy and safety of intravenous immune globulin, however, compared with plasma exchange and prednisone therapy, for either chronic inflammatory demyelinating neuropathy or myasthenia gravis have not yet been established by controlled clinical trials.

JOHN C. KEESEY, MD
Long Beach, California

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Botulinum Toxin Therapy

BOTULINUM TOXIN is a potent neurotoxin that binds to the extracellular portion of the nerve terminal membrane and inhibits transmission across the neuromuscular junction. The effect of the toxin is gradual, lasts for several months, and can lead to denervation atrophy of the involved muscle. Doses of botulinum toxin are expressed in mouse median lethal dose (LD_{50}) units. The first therapeutic application of botulinum toxin was in strabismus. Botulinum toxin is most useful for strabismic angles of less than 50 prism diopters, postoperative residual strabismus, paralytic strabismus, and cases where surgical intervention is inappropriate. In a few pa-

tients, retrobulbar hemorrhage, eye perforation, double vision, and spatial disorientation may occur. The toxin is also used for spastic entropion, blepharospasm, and hemifacial spasm. The treatment of hemifacial spasm and blepharospasm requires about 25 units. The therapeutic effect lasts, on average, three to four months.

Botulinum toxin therapy is beneficial in spasmodic torticollis. Though improvement could be delayed for as long as two to six weeks, the effect usually starts on the second day, peaks during the first week, and lasts for three months. The treatment of torticollis requires an average of 200 units of toxin, and electromyographic guidance is necessary when deep muscles are injected. Side effects are mild and infrequent and include swallowing difficulties, a temporary increase in spasm or jerking movements, floppy neck, and dysphonia. In one patient, brachial plexopathy occurred after botulinum toxin was administered, and immunologically mediated reactions were suggested. Antibodies to the toxin may develop, rendering further treatment ineffective.

In patients with adductor spasmodic dysphonia, which is characterized by strenuous speech with a staccato, jerky, squeezed, hoarse, groaning voice, administering a small amount of toxin into the laryngeal muscle has been effective. Initial studies used higher doses, but in clinical practice now, only about 5 units are used. Side effects include swallowing difficulties, choking, or a breathy voice, which may last for one or two weeks. An improved voice quality lasts from three to six months after the treatment.

Although botulinum toxin can also be used in treating oromandibular dyskinesia, its use in lingual dystonia should be approached with caution, as it may interfere with swallowing. Other successful applications of botulinum toxin include the treatment of writer's cramp and detrusor sphincter dyssynergia.

DANIEL D. TRUONG, MD
Orange, California

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Preventing Chemotherapy-induced Neuropathy

TREATMENT WITH a number of chemotherapeutic drugs is well recognized to result in acute or chronic neurologic injuries. In the evaluation of patients with these injuries, the clinical neurologic examination and testing can be of major importance to reduce or alter the effects of such agents on the peripheral nervous system. In general, the sensory nerve fibers of the peripheral nerves are more susceptible to injury than are the motor or autonomic peripheral nerve structures.

The feet are most commonly affected, and patients usually have numbness, tingling, dysesthesias, or burning sensations. Dysfunction occurs to the dorsal root ganglia or to the peripheral nerve structures directly. On clinical examination, there may be altered sensation to light touch, cutaneous hypersensitivity, or the results may be normal. Large-fiber sensory dysfunction can be evaluated by testing vibration, proprioception, and kinesthetic perception as well as detecting reduced motor reflexes.

It is essential to evaluate patients by clinical examination before starting chemotherapy. Many patients, particularly elderly persons, may have silent peripheral polyneuropathies from other causes such as alcoholism, nutritional disorders, metabolic problems, and degenerative causes. Some patients may have a remote effect on their peripheral nerves as a result of a paraneoplastic syndrome.

Electrodiagnostic studies can be helpful to determine the extent or progression of a neuropathy. Sensory amplitudes, waveform analysis, latencies, and conduction velocities are the most sensitive studies early in the illness, whereas motor conductions and electromyograms may only become abnormal as the problems progress. Dermatomal cutaneous evoked potentials and automated semiquantitative measures of vibratory and thermal sensations can also be used to evaluate peripheral nerve function.

Several therapeutic agents are known to cause peripheral nerve dysfunction, cisplatin being a classic example. The neuropathy is similar to that caused by vitamin E deficiency, and efforts have been made using agents such as ethiofos, adrenocorticotropin analogues, and vitamin E to reduce its severity. Other agents such as vincristine sulfate can produce an autonomic neuropathy with a main presentation of postural hypotension in addition to the polyneuropathy.

Patient instructions are paramount for the early detection of adverse neuropathies associated with chemotherapy. General treatment measures include discontinuation of the drugs, the recognition of underlying treatable neuropathies, and symptomatic treatment.

KENNETH L. NUDLEMAN, MD
Orange, California

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Carotid Endarterectomy

THE BENEFIT OF CAROTID ENDARTERECTOMY in preventing stroke is now being clarified by well-conceived randomized trials, 38 years after the procedure was first performed.

The original study of the efficacy of carotid endarterectomy was published in 1970. This is not considered a definitive trial because of design imperfections and a perioperative mortality and morbidity rate of 11%. The strongest trend in the study was toward a benefit for patients with a vessel diameter reduction of 50% or more. Notable stenosis is variously defined as a diameter reduction of 50% to 70% or greater. The method of quantitation is disputed, but higher degrees of stenosis have been the most widely accepted indication for the procedure, particularly in patients with appropriate symptoms.

In 1985 about 107,000 endarterectomies were done in the United States. At the same time, the procedure was criticized as unsubstantiated and overused. Also in 1985, the negative

results of the Extracranial-Intracranial Bypass Study Group were reported. Because of these events, indications for carotid endarterectomy were reevaluated and randomized trials proposed. There are now six trials in progress: two symptomatic trials in North America, one in Europe, and three asymptomatic trials in North America. In 1987 the number of endarterectomies done in this country had fallen to 81,000 and is even lower now.

The Rand Corporation has recently applied consensus methods to derive indications for doing carotid endarterectomy. The investigators surveyed a panel of nine "experts" in several disciplines on the indications for the procedure in a large number of clinical scenarios. Though consensus was not obtained in all scenarios, a remarkable degree of agreement did develop. Endarterectomy was deemed indicated for minor stroke or two or more transient ischemic attacks with or without aspirin therapy if there was a diameter reduction of 70% or greater or 50% or more with a large ulcer. The procedure was considered indicated in asymptomatic patients only in the presence of unilateral occlusion and contralateral 70% or more stenosis. In both symptomatic and asymptomatic patients, surgical treatment was assumed to be a low to medium risk. This consensus analysis has resulted in a position paper by the American College of Physicians.

A preliminary report from the North American Symptomatic Carotid Endarterectomy Trial indicates that endarterectomy is considerably better than medical therapy (usually aspirin) in reducing the incidences of death and of stroke in symptomatic patients with a stenosis of 70% or greater. Similar results have been found in the European study, which also found that the procedure was not as effective as medical therapy for those with a stenosis of less than 30%. These two trials continue for those with stenoses between 30% and 69%. There are no reports from the three trials for asymptomatic patients.

Other characteristics of the atherosclerotic plaque at the carotid bifurcation may be important to stroke production, but this has not been proved, and their characterization by current arteriographic and ultrasonic techniques is uncertain.

In summary, carotid endarterectomy is currently being done less often than six years ago, and interest is focused mostly on relating degree of stenosis to outcome. Plaque characteristics are probably also important and are being studied.

GREGORY K. CALL, MD
Salt Lake City, Utah

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Alerts, Notices, and Case Reports

Intravascular (Angiotropic) Large-cell Lymphoma ('Malignant Angioendotheliomatosis') With Small Vessel Pulmonary Vascular Obstruction and Hypercalcemia

JEFFREY L. CURTIS, MD
Ann Arbor, Michigan

MARTHA L. WARNOCK, MD
DOUGLAS J. CONRAD, MD
LISA K. HELFEND, PhD, MD
HOMER A. BOUSHEY, MD
San Francisco, California

INTRAVASCULAR (ANGIOTROPIC) LYMPHOMA is an uncommon syndrome defined pathologically by massive neoplastic proliferation of lymphoid cells within the lumens of capillaries and small veins and arteries, with little or no adjacent parenchymal involvement.[1,2] The syndrome is usually manifested clinically by fever, nonlocalizing neurologic signs or dementia, and cutaneous nodules or plaques.[1] Although autopsy findings show the lungs are frequently involved along with other organs, prominent pulmonary symptoms are unusual.[2-5] We describe a case of intravascular lymphoma in which the patient had hypercalcemia, with the presentation dominated by dyspnea and unexplained hypoxemia. Pulmonary function testing and imaging suggested microscopic pulmonary vascular disease, most likely due to tumor emboli. An autopsy disclosed widespread intravascular and limited parenchymal large-cell lymphoma, with a previously undescribed angiitis restricted to the pulmonary vessels.

Report of a Case

The patient, a 76-year-old Guatemalan man, was admitted in March 1989 for dyspnea and confusion. Four months previously, persistent abdominal pain and anorexia had developed, followed by a 13.6-kg (30-lb) weight loss, fatigue, and difficulty concentrating. A serum calcium level of 3.82 mmol per liter (15.3 mg per dl) was noted, and he was admitted to the hospital in February 1989.

First Admission

The patient was a retired carpenter who had immigrated to the United States in 1968. He had formerly smoked cigarettes (30 pack-years total) but quit 13 years ago. There was no history of an excessive ingestion of dairy products, vitamin D, or calcium-containing antacids. A physical examination was unrevealing except for drowsiness and disorientation for time and place. A chest radiograph showed only right apical pleural thickening. The results of the following tests were normal: complete blood count with differential cell fraction; liver function tests; blood urea nitrogen, creatinine, and serum electrolytes; computed tomography of the head (with and without contrast); bone scan, acid phosphatase, and serum and urine protein electrophoresis; both ultrasonography and computed tomography of the neck; and barium swallow with upper gastrointestinal study, abdominal ultrasonography, and barium enema. The parathormone level was normal on two occasions. He was treated with a regimen of intravenous saline solution, furosemide, and subsequently etidronate disodium. The hypercalcemia resolved over several days, his mental state improved, and the abdominal pain diminished. The patient was discharged home on a regimen of furosemide and etidronate disodium. Over the next three weeks, dyspnea, increased fatigue, headaches, and myalgias developed and he had worsening confusion. Occasional auditory and visual hallucinations were reported, and he was readmitted to the hospital in early March.

Second Admission

On physical examination the patient appeared chronically ill and was in mild respiratory distress. His temperature was 36.8°C (98.2° F), blood pressure 100/56 torr, pulse 80 per minute, and respiratory rate 20 per minute. No lymphadenopathy or skin lesions were noted. Both lungs had crackles without consolidation or wheezes. The findings of the cardiovascular and abdominal examinations were normal, and a spleen tip was not felt. Stool specimens were negative for occult blood. He was somnolent and disoriented as to time and place, but no focal neurologic findings were noted. A urinalysis was normal. The leukocyte count was 3.2×10^9 per liter (0.52 neutrophils, 0.14 lymphocytes, 0.15 monocytes, 0.003 eosinophils, 0.003 basophils, and 0.18 atypical lymphocytes). The hemoglobin was 146 grams per liter, the platelet count 102×10^9 per liter, and the erythrocyte sedimentation rate 19 mm per hour. Serum electrolytes were normal with a calcium level of 2.35 mmol per liter (9.4 mg per dl) and a phosphorus level of 1.74 mmol per liter (5.4 mg per dl). Liver function studies were normal with an albumin level of 33 grams per liter. Arterial blood gas determinations with the patient breathing room air showed pH 7.47, P_{CO_2} 3.33 kPa (25 torr), and P_{O_2} 6.91 kPa (52 torr). A chest radiograph was unchanged.

The patient was placed on supplemental oxygen therapy, and his hypoxemia resolved but not his confusion. A lumbar puncture revealed an opening pressure of 160 mm of water, protein level 0.79 grams per liter (79 mg per dl), glucose 3.05 mmol per liter (55 mg per dl), erythrocytes 11 per μl, leukocytes 7 per μl (all mononuclear), and no malignant cells. Culture of specimens of blood, urine, and cerebrospinal fluid was negative for pathogens. Spirometry and lung volumes were normal, but the diffusing capacity was 14.6 $ml \cdot min^{-1} \cdot torr^{-1}$ (63% of the predicted value). A radionuclide lung scan showed normal ventilation and multiple bilateral subsegmental perfusion defects (Figure 1). A Doppler examination of the lower extremities did not suggest venous

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From the Departments of Medicine (Drs Curtis, Conrad, and Boushey) and Pathology (Drs Warnock and Helfend) and the Cardiovascular Research Institute (Drs Curtis, Conrad, and Boushey), University of California, San Francisco, School of Medicine, and the Respiratory Care Section, Medical Service, Veterans Affairs Medical Center (Dr Curtis), San Francisco, California. Dr Curtis is now with the Department of Veterans Affairs Medical Center, Ann Arbor, Michigan.

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Reprint requests to Martha L. Warnock, MD, Respiratory Care Section (111D), VA Medical Center, 4150 Clement St, San Francisco, CA 94121-1598.

Figure 1.—A perfusion lung scan shows multiple patchy subsegmental defects. The accompanying ventilation scan was normal.

thrombosis, and a pulmonary angiogram was normal with a mean arterial pressure of 13 torr. An echocardiogram with air-bubble contrast showed no evidence of intracardiac thrombus or shunt. Computed tomography of the chest and abdomen showed wedge-shaped lesions in the spleen consistent with infarcts; no adenopathy was noted.

During the next week, the dyspnea persisted and mild pancytopenia developed (Table 1). Smears of the peripheral blood showed persistent atypical lymphocytes but no malignant cells or microangiopathic changes. Serologic testing for the human immunodeficiency virus was negative. On the 11th hospital day, the patient was placed empirically on high-dose steroid and antituberculous therapy. High-resolution computed tomography of the chest showed no evidence of interstitial lung disease or emphysema. A bone marrow aspirate showed lymphoma. The next day, the patient was noted to have a right hemiparesis. Over the next 36 hours he became markedly hypoxemic despite maximal oxygen delivery, and he died on the 17th hospital day.

Antibodies and Lectins

The monoclonal antibodies and lectins used, together with their specificities, are shown in Table 2.[6] Reagents were obtained from the following vendors: LCA, UCHL-1, L26, antilysozyme (muramidase), and anti-factor VIII-related antigen from DakoPatts (Santa Barbara, Calif); LN 1 from Clonab Biotest Diagnostics (Fairfield, NJ); LN 3 from ImmunoBiologics (Lisle, Ill); Leu-4 and Leu-M1 from Becton Dickinson & Co (Mountain View, Calif); and peanut *(Arachis hypogaea)* agglutinin and *Ulex europaeus* I lectin from E-Y Laboratories (San Mateo, Calif). To stain for keratins, we used a mixture of monoclonal antibodies: hybridoma clones AE-1 and AE-3 from Hybritech, Inc (San Diego, Calif) and hybridoma clones against 39-kd, 43-kd, and 50-kd keratin antigens from Becton Dickinson & Co.

Methods

Organs were fixed overnight in 10% buffered formalin solution (pH 7.0), except the brain, which was fixed for ten days in 20% formalin. Paraffin-embedded tissues were examined histologically with stains including hematoxylin and eosin, Verhoeff's-van Gieson, and chloroacetate esterase. Some sections of spleen and bone marrow were fixed in 4% paraformaldehyde solution, embedded in methacrylate, and cut at 2-μm thickness. Immunoperoxidase and lectin peroxidase stains were used on tissues embedded in either paraffin or plastic, using a modification of the avidin-biotin-peroxidase complex (ABC) method.[7] Sections were protease-digested for all stains except L26, UCHL-1, and antilysozyme. Diaminobenzidine was used as chromogen and hematoxylin as counterstain. In negative control tests, we substituted normal rabbit or mouse serum for the primary antibody. Appropriate positive control tissues were stained concurrently.

TABLE 1.—*Hematalagic Data in Elderly Man With Intravascular Lymphoma*

Admission	*Hemoglobin, grams/liter*	*Leukocyte Count, × 10⁹/liter*	*Platelet Count, × 10⁹/liter*
First	167	5.7	267
Second*	145	3.2	102
Day 7	90	2.5	94

*The second admission occurred 25 days after the first.

Autopsy Results

At a full autopsy performed 14 hours after death, the lungs (1,125 grams combined) were uniformly soft. Slices of the perfusion-fixed lung showed ill-defined linear markings in the periphery of all lobes. The heart (370 grams) had a sealed foramen ovale. The cut surface of the spleen (545 grams) showed total effacement of the splenic architecture and several grey subcapsular infarcts. The kidneys showed many ill-defined, bulging grey nodules as much as 0.5 cm in diameter scattered throughout the cortex. The parathyroid glands, abdominal and mediastinal lymph nodes, and adrenal glands were unremarkable. Sections of both frontal lobes and of the left occipital lobe of the brain had scattered hemorrhages 0.5 cm in diameter.

On histologic examination, the spleen was diffusely infiltrated by large-cell lymphoma; the bone marrow had focal vascular and extravascular involvement. Cytologically similar malignant cells were found in clumps or interspersed among erythrocytes and fibrin strands in capillaries and small veins and arteries throughout the body. Many of these vessels also showed thin perivascular cuffs of lymphocytes and histiocytes. Vessels in the grey and white matter of the brain and spinal cord that were partially or completely occluded by tumor were often associated with perivascular hemorrhages, hemosiderin pigment, or small ischemic in-

TABLE 2.—*Immunaperaxidase Staining af Tumor Cells*

Monoclonal Antibody or Lectin	*Cells Antibody Present on*	*Reactivity/ Organ**
LCA (CD45)†	All leukocytes	Pos/brain
LN 1 (CDw75)	Mature B cells, some T cells	Pos/brain
LN3 (HLA-DR)	B cells, activated T cells	Pos/spleen
L26	B cells	Pos/brain, adrenal
UCHL-1 (CD45RO)	Some T cells	Neg/spleen
Leu-4 (CD3)	All T cells	Neg/spleen
Leu-M1 (CD15)	Monocytes, neutrophils	Neg/brain
Antilysozyme	Monocytes, macrophages	Neg/adrenal
Peanut agglutinin	Germinal center B cells, FDC	Neg/adrenal, brain
Anti-factor VIII	Endothelial cells	Neg/brain‡
Ulex europaeus I	Endothelial cells	Neg/adrenal
Antikeratin	Epithelial cells	Neg/brain, adrenal

FDC = follicular dendritic cells, Neg = negative, Pos = positive

*Results of immunoperoxidase staining versus tissue tested
†Specificity of antibodies in clusters of differentiation as defined by the 4th International Workshop on Human Differentiation Antigens (Knapp et al)[6]
‡See Results section of text.

farcts. In the liver, patchy chronic inflammation and hepatocyte necrosis were associated with widespread involvement of sinusoids by tumor. Lymphoma was also present in adrenal sinusoids and in the renal cortical nodules. Review of the last peripheral blood smears, taken ten days before death, confirmed the absence of neoplastic cells.

In the lungs, small arteries and veins as much as 1 mm in diameter showed segmental angiitis in all stages of development (Figure 2-A and 2-B). Acute changes consisted of subendothelial tumor cells, endothelial cell hypertrophy, intimal hyperplasia, and focal destruction of media and elastic laminae, as seen in elastic tissue stains (Figure 2-B). Chronic inflammatory cells infiltrated the walls, but adventitial cells were sparse. Lumens contained noncohesive tumor cells and karyorrhectic cell debris. Chronic changes consisted of hyaline intimal fibrosis, sometimes creating two or three lumens resembling a recanalized thrombus. There was never evidence of recent intravascular thrombosis or of fibrinoid necrosis. Inflammatory cells were sparse. The linear interstitial markings noted grossly corresponded to scars of loose vascular connective tissue that were centered around small arteries and veins and radiated into alveolar walls. Metaplastic epithelium lined some of the scarred air spaces. Given the vascular changes, these scars were probably caused by ischemia.

The tumor cells were large, with moderate cytoplasm and irregular, vesicular nuclei that were sometimes deeply indented. One or two large nucleoli were present. Occasionally a giant cell with a single lobulated nucleus was encountered. Mitoses were frequent, both in vascular lumens and in parenchymal deposits. The final diagnosis was diffuse intravascular and parenchymal large-cell lymphoma with pulmonary angiitis.

Immunohistochemical Results

The results of immunohistochemical staining indicated that the neoplastic cells were of B-lymphocytic lineage (Table 2, Figure 2-C). Tumor cells did not react with markers of endothelial, epithelial, or other leukocytic lineages, including the chloroacetate esterase stain for myeloid cells. Factor

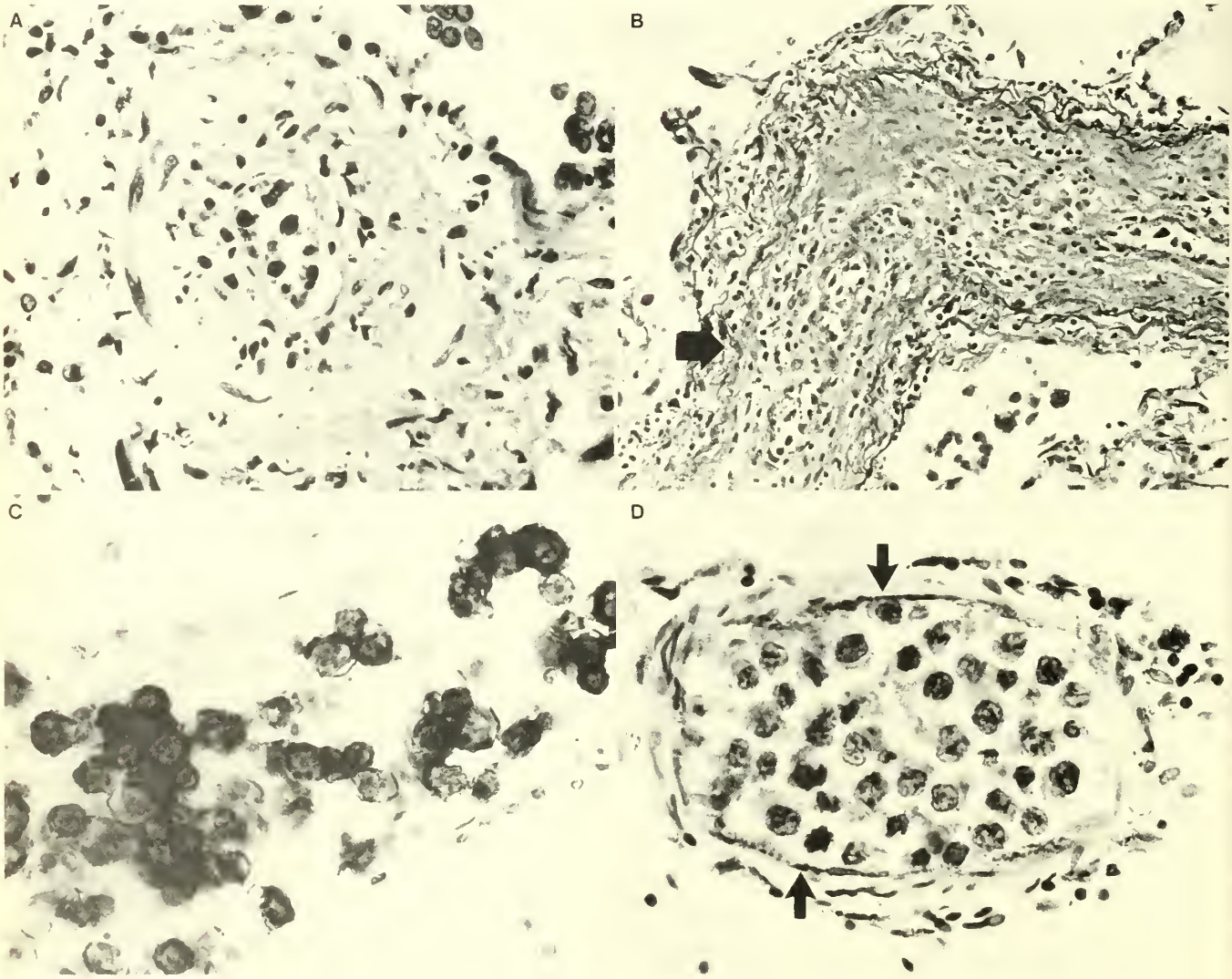

Figure 2.—The following histopathologic changes were found in blood vessels: **A,** A small pulmonary vessel (110 μm diameter) shows luminal narrowing by intimal thickening with scattered inflammatory cells (hematoxylin and eosin stain, original magnification × 500). **B,** A small muscular pulmonary artery (165 μm diameter) shows transmural inflammation with intimal proliferation and destruction of media and elastic laminas **(arrow)** (elastic van Gieson stain, original magnification × 200). **C,** A cerebral vessel stained by the immunoperoxidase method shows that the tumor cells react with L26, a B-cell marker (original magnification × 500). **D,** A cerebral vessel stained by the immunoperoxidase method shows reactivity of factor VIII-related antigen confined to the endothelial cells **(arrows).** The vessel is filled with large noncohesive lymphoma cells that are unreactive (original magnification × 500).

VIII-related antigen was present on endothelial cells and occasionally on extracellular material in the lumen, making interpretation difficult. Most vessels, however, contained tumor cells that were clearly nonreactive (Figure 2-D).

Discussion

This patient had a brief illness characterized by hypoxemia, transient hypercalcemia, confusion, and fever. Postmortem studies disclosed intravascular and occasional parenchymal large-cell lymphoma, consistent with the rare syndrome initially called angioendotheliomatosis.[8] This name reflected the belief that the malignant cells were of endothelial origin.[9] More recently the disorder has been shown to consist of two unrelated entities: one benign and cutaneous, the other malignant and systemic.[8] Recent analyses of surface antigen expression and immunoglobulin gene rearrangement have indicated conclusively that the malignant disorder is a true lymphoma.[10,11] The preferred name is now intravascular or angiotropic lymphoma.[2] Most cases appear, like the present case, to be of the B-cell lineage, although T-cell cases have been described.[12] Our case was clinically consistent with previous cases of intravascular lymphoma. Some findings that were unexplained before death, such as dementia, myalgias, and abdominal pain, were probably due to widespread microscopic vascular occlusion by tumor cells. The two striking clinical features, however, were the hypercalcemia and the dyspnea with progressive hypoxemia.

Hypercalcemia, noted when the patient was first seen, has been mentioned previously in only one patient with intravascular lymphoma.[5] At autopsy in our patient, the bones showed minimal scalloping of resorption but no active osteoclastic or osteoblastic activity. The results of parathormone assays and the rapid response to etidronate disodium, which blocks the action of osteoclasts directly, suggest a humoral hypercalcemia of malignancy.[13] The exact cause of the hypercalcemia is unclear and may have been multifactorial. It could have resulted from increased metabolism of vitamin D, as previously reported in lymphomas,[14] or from osteoclast-activating cytokines such as interleukin 1, lymphotoxin, or tumor necrosis factor secreted directly by the tumor or in response to it.[13]

Progressive hypoxemia has rarely been reported in previous cases of intravascular lymphoma. In almost all such cases, the chest radiographs have been diffusely abnormal, simulating interstitial lung disease.[2,3,5] In contrast, the case of a patient with a normal chest radiograph but profound hypoxemia as well as pulmonary hypertension due to intravascular lymphoma was reported by Snyder and associates.[4] In that patient, autopsy revealed pronounced intravascular tumor involvement in the lungs. Our patient's profound hypoxemia appeared to be related not so much to actual intrapulmonary tumor burden, which was less conspicuous than elsewhere in the body, as to the pulmonary angiitis and resulting vascular narrowing.

Not previously described, this angiitis was confined to the lungs and included all stages of development. It consisted of a prominent pleomorphic infiltrate of benign inflammatory cells, segmental necrosis, and fibrous vascular narrowing. Our patient's vascular process resembled the angiitis seen in some typical (nonintravascular) large cell lymphomas of the lungs, as well as in the controversial disorder, lymphomatoid granulomatosis.[15,16] Similar proliferative angiitis also occurs in Wegener's granulomatosis, in chronic infections, and in several rheumatologic diseases and need not be confined to the lungs.[17] In all these diseases the angiitis probably develops because of the local release of inflammatory mediators or growth factors, although the precise trigger for the release is unknown and may differ among conditions. In our patient, such mediators could have been released either by the tumor itself or as a reaction to the tumor cells, especially to tumor sequestered beneath the endothelium. Intimal proliferation in relation to intravascular lymphoma was noted recently by Yousem and Colby, although they did not describe pulmonary angiitis.[5]

A central question about intravascular lymphoma is why the malignant cells remain predominantly intravascular, unlike the cells in most large-cell lymphomas. Lymphoma cells enter lymph nodes in the same manner as normal lymphocytes, by means of adhesion (homing) receptors that recognize vascular addressins on high endothelial venules.[18-20] Ferry and co-workers investigated the hypothesis that intravascular lymphoma results from an absence of homing receptors on the malignant cells. Paradoxically, they found that all three cases examined expressed the antigen defined by the monoclonal antibody Hermes-3, thought at the time to be a specific lymphocyte homing receptor.[10] It is now recognized that this antigen (CD44) is a widely distributed adhesion molecule that appears to serve only an accessory role in the attachment of lymphoid cells to high endothelial venules.[21,22] Jalkanen and colleagues recently reported that the β-chain common to the leukocyte integrins (CD18) was absent or only weakly expressed on malignant cells in three cases of intravascular lymphoma.[23] Although the leukocyte integrin LFA-1 (CD11a/CD18) has been shown to contribute to extravasation of normal lymphocytes,[24] as noted by these authors, it is unlikely that intravascular lymphoma results from this defect alone. Patients with genetic defects in the expression of CD18 have the phenotype known as leukocyte adhesion deficiency, which is not associated with abnormal lymphocyte trafficking.[25] Moreover, malignant cells in routine non-Hodgkin's lymphomas are not infrequently CD18-negative.[26] Thus, it is still possible that the malignant cells in intravascular lymphoma lack specific homing receptors. Alternatively, molecular defects may reside in steps distal to the initial binding of lymphoma cells to endothelial cells. Thus, this rare syndrome may hold the answers to a number of fundamental questions about lymphocyte-endothelial cell interactions.

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Resolution of Bowel Obstruction Due to Newly Diagnosed Inoperable Advanced Ovarian Cancer With Medical Therapy

THOMAS P. DRAKES, MD
Redding, California

About half of patients with ovarian cancer suffer bowel obstruction at some point in the course of their disease.[1] In most of these patients, bowel obstruction occurs late in the course of the disease and is relieved surgically in only about half.[2-4] Factors predicting a poor result with surgical therapy include advanced age, severe nutritional deficiency, a large volume of tumor, ascites, and the failure of previous therapy.[5]

A much smaller group of patients presents initially or soon after the diagnosis of ovarian cancer with tumor-related obstruction. These patients, not described separately in most surgical series, survive longer than expected. In the series of Clarke-Pearson and co-workers, 13% of their patients operated on for ovarian cancer with bowel obstruction had received no previous chemotherapy and were presumably newly diagnosed.[6] Five of six survived more than two months postoperatively. The frequency of inoperable bowel obstruction in patients with newly diagnosed ovarian cancer is low, at least in university centers from which series are reported.

Tunca describes a small series of such patients with newly diagnosed ovarian cancer and inoperable bowel obstruction treated with nasogastric suction, total parenteral nutrition, and cisplatin-based chemotherapy.[7] Six of seven patients responded to a median of 1.5 courses of chemotherapy with the resolution of bowel obstruction, with three deaths at 4, 9, and 11 months and three patients alive with follow-up of 2 to 11 months. Krebs and Goplerud mention from their large series the cases of three patients treated for bowel obstruction with combination chemotherapy, presumably after surgical treatment, who had prolonged intervals before subsequent episodes of obstruction.[8] Only fragmentary data exist to support the concept of effective, and not simply palliative, medical management of patients with inoperable obstruction.

In this report I describe the case of three patients seen consecutively by one medical oncologist in a small community hospital within a year. Each had newly diagnosed ovarian cancer with inoperable bowel obstruction and was treated with prolonged nasogastric suction, parenteral hyperalimentation, and cisplatin-based chemotherapy. All three patients responded to medical therapy with the resolution of obstruction, and two patients later underwent complete surgical cytoreduction. They are now—23 and 28 months from presentation—clinically disease-free following the completion of chemotherapy.

Report of Cases

Patient 1

This 76-year-old woman with several months of weight loss, abdominal pain, and distention underwent a laparotomy in November 1988. Ascites and a large volume of abdominal carcinomatosis with several levels of small bowel obstruction precluded a surgical correction of the obstruction, nor could cytoreduction be attempted. Biopsy specimens revealed metastatic papillary cystadenocarcinoma. A baseline CA 125 level was 1,490 units per ml. Postoperatively, she was found to have an obstructive pattern on abdominal films, and nasogastric suction could not be discontinued. Chemotherapy with cyclophosphamide, 1,000 mg per m^2, and doxorubicin (Adriamycin) hydrochloride, 60 mg per m^2, was given on day 8. Neutropenia with fever developed on day 18 and resolved on intravenous ceftazidime and vancomycin hydrochloride therapy. Total parenteral nutrition was begun on day 22 and continued for a month. Chemotherapy with cyclophosphamide, 500 mg per m^2, and Adriamycin, 35 mg per m^2, was repeated on day 50. Nasogastric suction was successfully discontinued, and she was discharged eating normally on day 56. She subsequently continued monthly courses of cisplatin and cyclophosphamide for eight months. Complete cytoreduction was done in September 1989, followed by five cycles of a regimen of carboplatin, 250 mg per m^2, and cyclophosphamide, 600 mg per m^2. Her CA 125 level has

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From the Oncology Service, Redding Medical Center, Redding, California, and the Division of Hematology Oncology, University of California, Davis, Medical Center, Sacramento.

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Reprint requests to Thomas P. Drakes, MD, 1355 East St., Redding, CA 96001

been normal since the operation. All chemotherapy was discontinued in February 1990, 15 months after the laparotomy, and she had a negative laparoscopy in July 1990. She remains free of evidence of disease, with a CA 125 level of 8 units per ml and normal findings on physical examination in March 1991, 28 months from diagnosis.

Patient 2

This 55-year-old woman with a 15-year history of schizophrenia presented in February 1989 with complete small bowel obstruction. Nasogastric suction was begun, and at an operation, massive ascites and abdominal carcinomatosis with multiple levels of small bowel obstruction were encountered. No attempt at a bypass of obstructed small bowel or cytoreduction could be made. Biopsy specimens revealed poorly differentiated mucinous cystadenocarcinoma. A 3-cm mass was palpable in the cul-de-sac, and a baseline CA 125 level was 43 units per ml with a normal carcinoembryonic antigen level. After the operation, total parenteral nutrition was begun and nasogastric suction was continued. On day 5 she received a regimen of cisplatin, 100 mg per m^2, and cyclophosphamide, 1,000 mg per m^2. Hyperalimentation was interrupted for a week because of fever and neutropenia, which responded to intravenous ceftazidime and vancomycin therapy. Chemotherapy with cisplatin, 100 mg per m^2, and cyclophosphamide, 500 mg per m^2, was repeated on day 33. Nasogastric suction and total parenteral nutrition were discontinued on day 43. A CA 125 level was 26 units per ml three months after the operation, and the mass in the cul-de-sac and ascites were no longer palpable. Eating well, she regained her normal weight.

At that point the patient refused any further treatment and was discharged. She failed to keep any follow-up appointments. She was again admitted with severe dehydration, massive ascites, acidosis, and gastrointestinal hemorrhage in December 1989 and died the following day.

Patient 3

The patient, a 60-year-old woman with a long history of alcoholism and chronic obstructive pulmonary disease, presented in May 1989 with abdominal distention and constipation. A computed tomographic scan of the abdomen showed multiple cystic abdominal and pelvic masses. Barium enema films revealed nearly complete obstruction of the transverse colon, and on chest x-ray film a large left pleural effusion was seen. The CA 125 level was 1,950 units per ml. She was taken to surgery on June 5, but only a biopsy of extensive abdominal carcinomatosis and a transverse colostomy were done. Postoperatively, total parenteral nutrition and nasogastric suction were continued, but she still showed evidence of bowel obstruction with dilated loops of small bowel, poor colostomy output, and hyperactive bowel sounds. Respiratory distress due to massive ascites and left pleural effusion responded to oxygen therapy and thoracentesis. Biopsy specimens from the operation revealed poorly differentiated adenocarcinoma.

On day 15 she received chemotherapy with cyclophosphamide, 500 mg per m^2, and cisplatin, 100 mg per m^2. Her course was complicated by episodes of respiratory distress, massive anasarca, and oliguria. Bowel function improved within one week of chemotherapy, and she was discharged on day 23 taking oral food and fluids well. Her CA 125 level dropped to 970 units per ml, and the pleural effusion, ascites, and abdominal masses resolved with the first course of chemotherapy.

Chemotherapy was continued in monthly courses through September 1989 with the same doses of cyclophosphamide and cisplatin.

Complete surgical cytoreduction was done in mid-October. Her course has been complicated by moderate peripheral neuropathy, an episode of deep vein thrombophlebitis requiring anticoagulants, and acute cholecystitis requiring surgical intervention. She has received six more courses of chemotherapy since the cytoreduction. A CA 125 level was 14 units per ml in December 1989 and remains normal. She is felt for medical reasons not to be a candidate for surgical restaging. At the last follow-up visit in April 1991, she remained free of evidence of disease, with a CA 125 level of 21 units per ml and normal findings on physical examination, 23 months from presentation.

Discussion

This report of the successful medical treatment of patients with inoperable bowel obstruction complicating newly diagnosed ovarian cancer adds to the meager literature addressing treatment for this group of patients. The incidence and outcome of this set of circumstances cannot be easily discerned from the published series of patients treated for bowel obstruction from ovarian cancer, as these patients are rarely described separately from the rest, in most of whom bowel obstruction developed as a late manifestation of chemotherapeutic failure. Patients with newly diagnosed cancer deemed inoperable may be more common in community practice than in series published from university hospitals.

This report and that of Tunca[7] suggest that therapy with prolonged nasogastric suction, total parenteral nutrition, and cisplatin-based chemotherapy can salvage a substantial number of these patients. Beyond short-term survival in terms of discharge from the hospital eating normally, some of these patients may go on to receive adequate cytoreductive surgical therapy and may have the same long-term survival that can be expected from optimally applied de novo surgical cytoreduction and aggressive chemotherapy. These findings should be extended and confirmed in a larger number of patients through prospective cooperative trials, perhaps comparing surgical with medical therapy in patients with newly diagnosed ovarian cancer presenting with bowel obstruction, a group in whom initial surgical cytoreduction is difficult at best. A positive therapeutic approach even to the poorest risk patient is justified.

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Intractable Hiccups as a Presentation of Central Nervous System Sarcoidosis

LCDR JOHN P. CONNOLLY, MC, USN
LT TIMOTHY J. CRAIG, MC, USN
LCDR RAMÓN M. SANCHEZ, MC, USN
LCDR W. SCOTT SAGEMAN, MC, USN
LCDR ROBIN E. OSBORN, MC, USN
San Diego, California

HICCUPS ARE MOST OFTEN TRANSIENT and resolve without therapy. The differential diagnosis of persistent hiccups, however, is very long[1] (Table 1), and neurosarcoidosis has been suggested only once previously as a cause.[2] We report the case of a patient with biopsy-proven sarcoidosis in whom persistent hiccups developed as the first sign of recurrence in the central nervous system.

Report of a Case

The patient, a 25-year-old man, was diagnosed in May 1987 with uveitis, peripheral facial nerve palsy, and bihilar adenopathy on chest x-ray film. Sarcoidosis was diagnosed by transbronchial lung biopsy. A computed tomography (CT) scan and magnetic resonance imaging (MRI) of the brain were normal. The patient initially did well with a tapering course of prednisone over six months ending December 1987. In August 1988, he again sought medical care for weight loss, malaise, and persistent hiccups, which were unresponsive to multiple trials of metoclopramide hydrochloride, chlorpromazine hydrochloride, phenytoin sodium, and quinidine sulfate. A month later he noted bilateral lower extremity weakness and worsening of his hiccups. Physical examination showed a grossly ataxic gait and a notable (3 to 4/5) bilateral upper and lower extremity weakness. Urinary retention subsequently developed. A cranial CT scan was again normal. An MRI of the brain and spinal cord showed nodular thickening of the leptomeninges consistent with sarcoidosis (Figures 1 to 3). Polyneuropathy was evident on nerve conduction study results. The cerebrospinal fluid was remarkable for a protein level of 3,210 grams per liter, glucose level of 1.5 mmol per liter, and 248 mononuclear cells per μl. The patient was placed on a regimen of prednisone at 1 mg per kg per day for neurosarcoidosis. Within 48 hours his hiccups resolved. Over the next few weeks his motor strength increased and walking improved. Following three months of therapy, a repeat MRI also showed that the patient had improved.

TABLE 1.—*Commonly Reported Causes of Persistent Hiccups*

- Metabolic
  - Electrolyte imbalance
  - Renal failure
  - Alcohol ingestion
  - Diabetes mellitus
- Central nervous system
  - Tumors
  - Trauma or surgical procedure
  - Infections
  - Vascular lesions
  - Multiple sclerosis
- Peripheral nervous system (branches of vagus nerve)
  - Diaphragmatic irritation
  - Tympanic membrane irritation
  - Thoracic, ENT, or abdominal tumors
  - Thoracic, ENT, or abdominal infections
- Drugs
- Psychogenic
- Idiopathic

ENT = ears, nose, and throat

(Connolly JP, Craig TJ, Sanchez RM, Sageman WS, Osborn RE: Intractable hiccups as a presentation of central nervous system sarcoidosis. West J Med 1991 Jul; 155:78-79)

From the Departments of Internal Medicine (Pulmonary Division) (Drs Connolly, Craig, and Sageman), Neurology (Dr Sanchez), Radiology and Clinical Investigation (Dr Osborn), Naval Hospital, San Diego, California. Dr Connolly is currently with the Naval Hospital, Pensacola, Florida.

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Reprint requests to LCDR J. P. Connolly, MC, USN, c/o Clinical Investigation Department, Naval Hospital, San Diego, CA 92134-5000.

ABBREVIATIONS USED IN TEXT

CT = computed tomography
MRI = magnetic resonance imaging

Discussion

Approximately 5% of patients with sarcoidosis have neurologic involvement.[3-5] In half of these patients, the neurologic manifestation is the initial presentation of the overall disease.[3,5,6] Many of the neurologic manifestations of sarcoidosis, especially cranial nerve palsies and endocrine abnormalities, can be traced to basilar sarcoid meningitis.[7] Neurosarcoidosis has often been described as having a relapsing or remitting course. The unusual aspect of our case is the manifestation of recurrent disease. The largest series of patients with neurosarcoidosis[3,4] reports no cases of hiccups as a presenting problem. Souadjian and Cain reviewed 220 cases of intractable hiccups and outlined all associated diseases.[8] Only one patient in this large series was noted to have sarcoidosis. Lewis did not list sarcoidosis in more than 100 causes of persistent hiccups.[1] Kondo and co-workers reported a patient with sarcoidosis with persistent hiccups responsive to steroid treatment.[2] They attributed the hiccups to central nervous system involvement but were unable to confirm this by CT scan or MRI.

In our patient, the MRI showed meningeal involvement characteristic for sarcoidosis in the region of multiple cranial nerves as well as surrounding the presumed "hiccup center" in the midbrain or high cervical spinal cord. This region previously has been implicated on electromyography and other studies as being critical in the neural pathways involved in hiccups.[9,10] A cranial CT scan was not as sensitive for this process and did not establish the diagnosis. The response of neurosarcoidosis to steroid therapy has been reported to be variable,[1,5] but at least half of patients have a good clinical response to steroid therapy that may be long-lasting.[1] The rapid response of our patient's hiccups and his polyneuropathy to steroid therapy supports the contention that both symptoms were neurologic manifestations of sarcoidosis. Characteristic findings on MRI with improvement on repeated imaging during therapy helped to confirm this clinical impression.

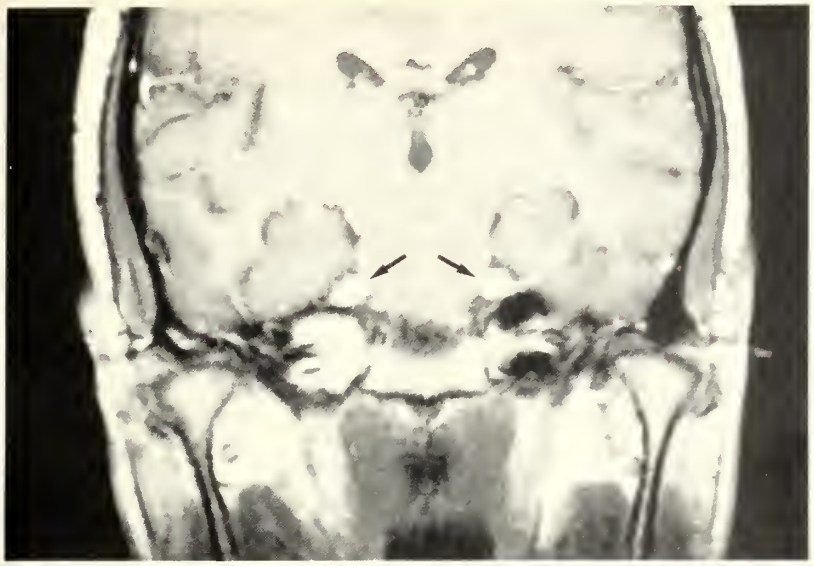

Figure 1.—A postgadolinium-enhanced coronal brain magnetic resonance image shows enlarged, enhancing fifth cranial nerves **(arrows)** (SE 500/20).

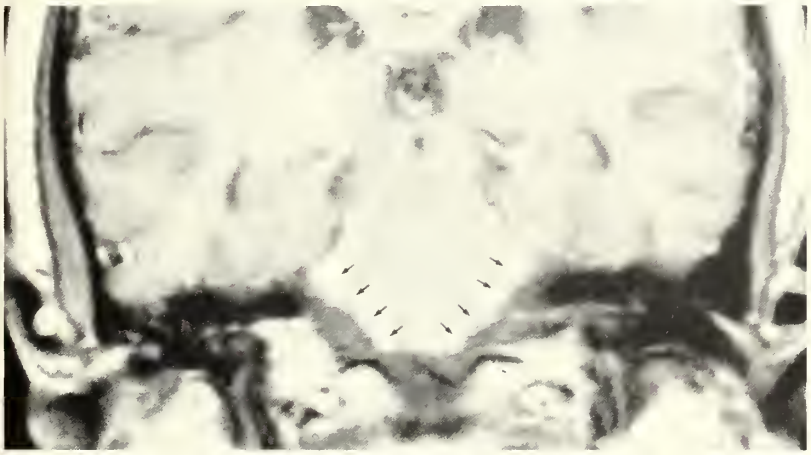

Figure 2.—The basilar meningeal involvement is seen as irregular, nodular gadolinium contrast enhancement **(arrows)** on this coronal brain image (SE 500/20).

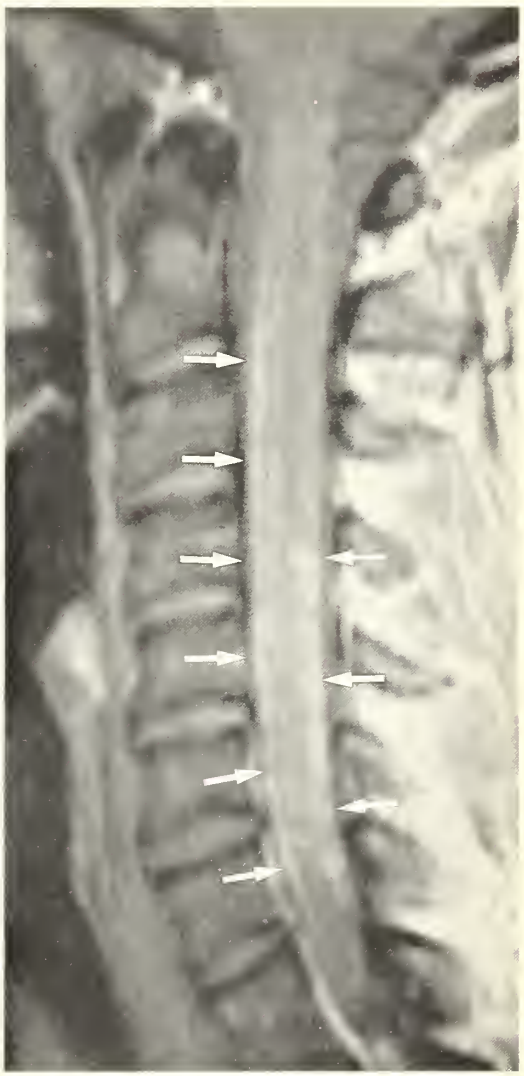

Figure 3.—A midline sagittal magnetic resonance image of the cervical spinal cord using gadolinium also shows nodular meningeal enhancement **(arrows)** (SE 800/20).

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Commentary

The Trial and Tribulation of Egerton Yorrick Davis

GERARD N. BURROW, MD, *La Jolla, California*

Every segment of society has and needs heroes, and Sir William Osler is without question the internist's hero. Through hard work and self-discipline, he instituted a scientific basis for clinical medicine and became the role model for clinical scientists. At the same time, part of him was an "imp of the perverse."[1(p49)] "An erratic spirit made him a perennial practical joker, provided a vehicle for his unquenchable ribaldry, and supplied many a nagging, and not completely answered, question in our efforts to evaluate the whole man."[1(p49)] In his later years, this side of Osler was expressed through his alter ego, Egerton Yorrick Davis.[2,3]

The "imp" was also present throughout his childhood and adolescence.[4] In 1864, at age 15, he was expelled from the Dundas (Ontario, Canada) Grammar School for a series of pranks, including locking a gaggle of geese in the rival public school overnight and removing all the desks and chairs from this school and putting them in the attic. The ultimate episode involved disparaging remarks about the public school's headmaster, which were repeated in the Dundas newspaper as a charge against his father, the Reverend Featherstone Osler. These escapades continued after he entered the Barrie (Ontario) Grammar School, where he quickly became the leader of "Barrie's bad boys"—three boarders who feuded with the day boys. Their pranks included covering a smoking chimney on the schoolhouse roof with a board and gleefully watching the arrival of the Barrie Hook and Ladder Company.[4]

After a year at Barrie, Osler was enrolled in Trinity College School in Weston. This church school was affiliated with Trinity University in Toronto and functioned on the model of an English public school. Osler flourished at Trinity but also became involved in several escapades, for one of which he and nine other students were tried on charges of assault. Although he may well have been the ringleader, the charges against him were dropped (*Toronto Globe*, April 9 and April 11, 1866, Toronto, Ontario [Figure 2]).

Ten Trinity College students were tried for assault and trespass on the widow of a clergyman before the County Magistrate, Mr S. Alcorn, Justice of the Peace, in Toronto on April 9, 1866. The trespass and assault were alleged to have been committed on March 29, 1866, at which time William Osler was almost 17 and a school leader, becoming head prefect the next year. In fact, three of the four prefects for the next school year, Osler, Jones, and Wilson, were among the defendants (Figure 1). One of Osler's brothers was the defense lawyer. Cushing states that it was Featherstone Osler, who later became one of Ontario's most respected judges.[5(pp29-31)] The *Toronto Globe* reported that Mr J. B. Osler appeared for the defense. It may actually have been another brother, Britton Bath Osler, who has been called the greatest criminal lawyer in Canadian history.

Mr Badgley, the headmaster of Trinity College School and also a clergyman, hired the widow, Mrs Denham, and her daughter to serve as housekeepers, and they occupied eight rooms on the second and third floors of the school. The

Figure 1.—Pictured are the four prefects at Trinity College School for the school year following the trial; Osler, Wilson, and Jones had been defendants. Standing, left to right: R.J. Wilson and William Osler; sitting, L.K. Jones and F.J. Helliwell (from the Trinity College School Record, *Jubilee* 1915; 17:63).

(Burrow GN: The trial and tribulation of Egerton Yorrick Davis. West J Med 1991 Jul; 155:80-82)

Dr Burrow is Professor of Medicine, Vice Chancellor for Health Sciences, and Dean, University of California, San Diego, School of Medicine, La Jolla
Peter Osler, QC, helped prepare this article.
Reprint requests to Gerard N. Burrow, MD, Vice Chancellor for Health Sciences, UCSD School of Medicine (0602), 9500 Gilman Dr, La Jolla, CA 92093-0602.

Toronto Globe
April 9, 1866

School Row at Weston

Pupils Turn Outlaws—They Fumigate The Matron
With Sulphur—Examination Yesterday

As announced yesterday, the case of assault committed on a Mrs Denham, by a number of youths at the Trinity College Grammar School, came off yesterday in the County Council Chamber, in the Court House, before Mr S. Alcorn, with Messrs Robert James Jr, Dr Berryman, and T.J. Preston as associates. The following boys were brought up: Robert Wilson, A. McCuaig, John Price, John Gray, Wm. and Jas. Johnston, Wm. Osler, John Fraser, and Forbes Whitney. Two others, named L.K. Jones and Arthur Holland, are in bed, ill, and did not consequently attend.

The information included the names of all the parties, but they were tried separately, Robert Wilson being brought up first.

Mr Moore appeared for the prosecution, and Mr J.B. Osler for the defence. A large number of spectators were present, who watched with interest the recital of the case.

[Transcript material deleted.]

Mrs H. DENHAM sworn: I reside at Weston; occupy the part above the school room. Mr Johnston put me in possession of the premises. I was to pay 25 pounds per annum. Witness then detailed the assault. Wilson was not one of them on the first assault on the 29th, between 8 and 9 a.m. Prisoner was there in the after part of the day and tied the door. Wilson was there on the 2nd attack. A rope was attached to my door, and witness held it about three feet from the door. This prevented my getting out. I think that the rope was fastened to the banister, cannot say positively. Wilson was pulling at the rope. I was struck with a snowball. Saw Wilson and the other boys throw snowballs into my room. One or two of the boys held the door open while the rest fired the balls in, enough almost to extinguish the fire. They forced the cover off the stove-pipe hole and flung wood in through it. I went to the door to assist in getting it open.

To the MAGISTRY: Wilson called the "old fool" and "old gray." I tried to reason with him.

To Mr OSLER: I threw something down the stairs after the boys.

[Transcript material deleted].

Wm. OSLER sworn—saw him on that day. He shook his fist in my face and said in a threatening manner "Now, old woman, tell me how much do you pay?" (Laughter) He was one of these who tied the door; he was amongst the rest. He said he wanted a leg of the "mortgaged piano." (Laughter) He was one of those present when the wood was thrown. I did not see him throw snow balls. He admitted that he had held the door. There were about a dozen sticks thrown up into the room.

Miss DENHAM testified: Saw this defendant on the stairs; he threw snowballs into my mother's apartments. He was present at the opening of my mother's door. He was ordered away. He threw several snow balls at my mother. He used insulting language. He asked for Mr Badgley's beer tap that had been stolen. (Laughter) Saw him in the rooms.

To Mr OSLER: All the boys were aiding in tying the room.

The case against this boy was dismissed.

Toronto Globe
April 11, 1866

The School Scrape at Weston

Evidence for the Defence—A Few of the "Youths"
Examined—They Are Reprimanded and Fined

[Transcript material deleted]

W. OSLER, a lad of 16, sworn: Said that Wilson had something to do with the tying of the door. Wilson, Jones, Price, Gray, Holland, Forbes, Whitney, McCuaig, and Perry, were present when the door was tied. John Frazer was not there; some of them were not interfering; I went to the school at a quarter to 9 o'clock. I don't remember any keys there. The rope tying took place at a quarter past 3. School was out at 12 o'clock. I was at the place at a quarter to 2 o'clock. All the boys were there except Holland and myself. I saw no sticks thrown up the stove-pipe, I saw no snowballs thrown either at Mrs Denham or at the door. I believe the boys used to go where they liked. The tying took place at a quarter past three. A slip knot was made in the rope and one of the boys put it over the knob of the door; there were screams in the room and someone fell back after the rope was cut. The rope was tied about one minute or so but it was held about 5 minutes. I did not hear Mrs Denham ask to have the door open. I felt some person trying to get out.

To Mr MOORE: I could not say how many boys were at the tying of the rope. I could not say there were more than five boys engaged at the tying of the door. I could smell smoke of sulphur. I did not recognize the smoke of sulphur on the stairs. The object of making smoke was that Mrs Denham might not go down to the kitchen without smelling it. The stove-pipe goes into the wall. The boys engaged in making the fumigation were most of the boys charged. I saw no boys break the clock. I saw a boy going up the clock. I told him to leave the clock alone. I saw no boy going to the preserve dishes. I don't know there were any preserve dishes there. The wood was cut at the parsonage in two lengths. I saw no wood at Mrs Denham's. I could not say whether the wood was cut once or twice. Mrs Denham had some of her cord wood removed into the kitchen.

[Transcript material deleted.]

This closed the evidence.

Mr MICHAEL then addressed the court for the defense and Mr Moore for the prosecution.

The Magistrate then retired to consider the evidence.

Having returned, Robert Wilson, Augustus McCuaig, John Gray, Wm. Osler, Peter Kemp, L.K. Jones, Wm. Johnston, and Forbes Whitney then stood up.

Mr ALCORN said that there were 12 defendants in this sad disreputable scrape, 2 are sick and 1 discharged. He was very sorry to see such conduct as had been recited, and if they did play it should be kept within legitimate bounds. It was not respectable to their parents to be found guilty of such tricks as had been played on an old woman. Mr Alcorn then strongly reprimanded them and stated that each of the defendants would have to pay a fine of $1 and costs.

The court then adjourned.

Figure 2.—Two accounts of Osler's "school scrape" at Weston are given.

mother and daughter were unpopular with the students. After the episode, the widow preferred charges of trespass and assault but, according to Cushing, was unable to get a warrant issued locally in Weston and finally secured one in Toronto.[5] Twelve students were named in the suit and were tried separately rather than as a group. Two of the boys were ill and not brought to trial. The case excited a great deal of interest, with crowded courtrooms and front page coverage in the two Toronto newspapers, the *Toronto Globe* and the *Daily Leader*.

Reconstructing the precipitating event is difficult because of conflicting accounts within and between the two newspapers, as well as the accounts of Cushing and the *Trinity College Record*. In Cushing's version in which he is repeating the story that came to him "from the little girl to whom stories of his boyhood used to be told by Sir William before the library fire in Oxford," the assault was revenge for the specific offense of Mrs Denham's having upset a pail of slops on the stairs, which soused one of the boys.[5(p30)] Cushing was aware of the *Toronto Globe* article. In the *Daily Leader* newspaper account, however, Mrs Denham said she threw the slops down the stairs on the boys in response to the assault (*Daily Leader*, April 10 and April 11, 1866). The headmaster, Mr Badgley, said the boys had told him that "Mrs Denham had distributed the contents of an article of bedroom furniture on their heads," but McCuaig's testimony indicates that this occurred after the trouble had started.

After hearing all the evidence, the magistrate, Mr Alcorn, found nine of the ten boys guilty and fined them $1 and costs. They were also bound over to keep the peace, especially to the Denhams. Mr Alcorn stated that he and his associate magistrates felt inclined to inflict a heavy fine but did not because the parents would suffer.

The case against William Osler was dismissed. No cause

for the dismissal of charges against Osler was given. His testimony implicated him as guilty as the other nine who were fined. In fact, Cushing states, "At Osler's *instigation*, they barricaded 'the old girl' in her sitting room."[5(p30)] Certainly, the escapade was entirely in character with the personality of Egerton Y. Davis and consistent with his past behavior. Osler's brother, in his role as defense attorney, may well have been responsible for the criminal record of Sir William Osler remaining unbesmirched.

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OUT IN THE TRENCHES

Physicians travailing in ivory towers
(Or medical meccas of mythical powers)
Find miracle cures as they sit at their benches,
In contrast to doctors prevailing in trenches.

When going gets tough in the ivory tower,
The tough call the intern at whatever hour.
But elsewhere there's no one to "just take a peek,"
And rowing gets rough when her hell springs a leak.

She places an order for second opinions;
They come back anemic, examined by minions.
And each brief alliance is summed by a clause:
"Unusual disorder of ill-defined cause

"Which bears good prognosis if patient avoids
Continued reliance on too much steroids."
So swiftly the ball is passed back to the trenches
From erudite coaches on masonite benches.

The team reassembles, but always in doubt.
She tapers the "monster"; the plug's not pulled out.
For out in the trenches, but not in defiance,
Most practical docs crystal ball-gaze with science.

But why does the other grass always seem greener?
Would time on the bench change her restless demeanor?
Complexity means that their patients are sicker;
Procedures and tests amass; charts volumes thicker.

Her patients are flour and salt of the earth,
Their workups are easy—like textbook childbirth.
Years pass in the trenches; they turn into friends.
Too quickly the tower relationship ends.

Up there, in most cases, the docs haven't yet
Mistrusted their science and gotten all wet,
While she is the lonely doc with muddy shoes.
She's trod in both places and therefore can choose.

ELIZABETH SPENCER SMITH, MD©
Santa Rosa, California

Editorials

Subacute Thyroiditis

SUBACUTE THYROIDITIS, which appears under a variety of synonyms such as de Quervain's or granulomatous thyroiditis, is a self-limited, destructive inflammation of the thyroid gland that is characteristically associated with severe pain and tenderness of that organ during the active phase of the disease. It is thought to be caused by infection with one of various potential viral invaders. Often it is preceded by pharyngitis that subsides a week or two before the symptoms of thyroiditis appear. Sometimes it is a relatively rare complication of common diseases, such as mumps or measles. It is differentiated from acute thyroiditis by its etiology and characteristics more than by its duration. Acute thyroiditis is a nosologic term traditionally reserved for bacterial inflammation of the gland, usually manifested as a localized abscess. Chronic thyroiditis, on the other hand, persists for many months or years, is rarely painful, and is usually due to the development of cytotoxic antibodies directed against a patient's own thyroid cells.

In most patients the diagnosis of subacute thyroiditis is made relatively easily from the history, physical and laboratory findings, and clinical course. In its early phase it is often associated with clinical and laboratory evidence of thyrotoxicosis due to massive destruction of the thyroid gland and the release of intrafollicular thyroglobulin, which is broken down into thyroid hormone extrathyroidally. In recent years, a high frequency of "painless" thyroiditis has been reported, particularly from the American Midwest. This is usually associated with a small or undetectable thyroid enlargement, extremely low thyroid radioiodine uptake, characteristic signs and symptoms of thyrotoxicosis (but without infiltrative ophthalmopathy), undetectable plasma thyroid-stimulating hormone levels, and elevated thyroid hormone concentrations. In some series the incidence of painless thyroiditis has been as high as 15% of all patients with thyrotoxicosis. In most other geographic areas, however, the incidence is much lower. In our experience it is rare.

Some cases of thyrotoxicosis with these laboratory findings in the Midwest have been established as thyrotoxicosis factitia caused by the ingestion of ground beef contaminated with thyroid tissue due to the inadequate training of personnel in a local abattoir. Differentiating thyrotoxicosis due to subacute thyroiditis from thyrotoxicosis factitia is ordinarily easy, however. The plasma thyroglobulin level is elevated in cases of the former because of extreme tissue destruction whereas it is low in cases of the latter; there is no thyroglobulin in thyroxine or triiodothyronine, and the thyroglobulin in desiccated thyroid will be digested in the gastrointestinal tract before absorption.

Nordyke and collaborators report in this issue of the journal their prospective observations over a 22-year period beginning in 1960 on 269 patients with painful subacute thyroiditis.[1] Unfortunately, the clinical course was followed in only 70 of these and there is some uncertainty about the adequacy of the criteria used for diagnosis because laboratory tests were employed only "when needed for confirmation." Most thyroidologists would feel that, although a tender mass in the thyroid area (the authors' only defined "typical" sign) is consistent with subacute thyroiditis, other possibilities exist, including hemorrhage into a preexisting thyroid nodule. A more consistent use of laboratory tests in the study would have alleviated concerns about the diagnosis because a high erythrocyte sedimentation rate and severely depressed thyroid radioiodine uptake are hallmarks of painful subacute thyroiditis and are not characteristic of other possibilities.

Accepting this diagnostic caveat, the data presented by Nordyke and co-workers are of demographic interest. Their general clinic population in Hawaii has a 2:1 white to Japanese ethnic ratio. This same ratio existed in their thyroiditis patients, and there was no racial difference in the sex predominance of female patients, the clinical course, or the onset of the disease in primarily young and middle-aged adults.

Certain differences in the frequency of thyroid disease between patients of Asian and European lineage are well known. Thyrotoxic periodic paralysis is seen much more frequently in the Asian population. Occult differentiated carcinoma of the thyroid found at autopsy in patients who died without clinically diagnosed thyroid disease is much more common in Japanese patients, regardless of their geographic residence, than in white Americans (25% versus 5%, respectively). Yet the death rate from thyroid cancer is comparably low at approximately 0.5 per 100,000 for both groups. Thus, Nordyke and associates have provided important data in documenting that there is no difference in subacute thyroiditis between these ethnic groups living on the same island.

Their observation that there was no seasonal difference in the frequency of newly diagnosed cases is also of interest because other investigators have variously reported that there is or is not a higher incidence of subacute thyroiditis during the summer months. Although one might question whether seasonal differences would be distinct in a mild climate like Hawaii's, no seasonal variation was found in studies from Minnesota and Finland where the periodic climatic contrasts are much more severe.

MONTE A. GREER, MD
Professor of Medicine
Section of Endocrinology
Oregon Health Sciences University
Portland, Oregon

REFERENCE

1. Nordyke RA, Gilbert FI Jr, Lew C. Painful subacute thyroiditis in Hawaii. West J Med 1991 Jul; 155:61-63

Two Medical Worlds—Separate and Unequal

IN AMERICA, we live in two medical worlds, the world that exists for those of us fortunate enough to take advantage of the science we can apply to human health, and the world that exists for the poor, the disenfranchised, the uneducated, and the unlucky. These worlds are separate and unequal, and the differences between them grow daily.

In many New York City municipal hospitals, a patient can wait in the emergency department for 48 hours before being admitted, not waiting for high technology therapy but rather because all the beds are full or there are not enough nurses to staff them. Those persons whose disease process places them at highest risk are given priority. This means if patients are sick but not immediately about to die, they wait.

Long waits exist not only in the emergency departments; they are everywhere. Newly diagnosed patients with the acquired immunodeficiency syndrome, for example, can wait

two to three months for an appointment at one of New York City's overburdened HIV clinics.

Working patients with good insurance coverage do not have to wait as long because virtually every private institution in the city discriminates on the basis of ability to pay. In other words, the admission of "paying" patients who have private physicians is encouraged, while the admission of nonpaying or marginal payment patients is diverted, delayed, or denied. Remember, it is only illegal to discriminate against nonpaying patients if there is a life-threatening emergency. Even then, the only requirement is that a hospital do its best to care for the emergency condition long enough to stabilize the patient for transfer to another facility.

Medical care at an inner-city institution has problems. There are long waiting lines for hospital admission or for getting a prescription filled. The equipment is older than the equipment in the private hospital down the street. Some of it will not work, so if the ophthalmoscope is broken and the patient needs an eye examination, or if the examination table does not work and the patient needs a pelvic examination, they will sit there until a room with needed equipment becomes available, thus slowing the process substantially. Physicians spend less time with patients and, during that time, will be much more rushed. If patients are seen by an intern or resident, it is less likely that an attending physician or one who has completed training will confirm the diagnosis and approve the treatment. And if a follow-up appointment is needed, it is unlikely that the patient will see the same physician again. The floor will be dirtier, the food colder, the lack of privacy greater.

And so we ask, why would anyone choose this health care? Why would someone put up with those differences? For most patients who are sick, who are in pain, who have no alternatives, that hospital may be a godsend. The mothers who know what happens when their children are not immunized will wait as long as it takes. Those pregnant women who know what it is like to lose a child or to have one born with serious health problems will wait as long as it takes to get their blood pressure checked, their vitamin prescription filled, and their examination. Poverty does not always mean ignorance and lack of self-esteem.

Patients who come to us from El Salvador, Sierra Leone, Nigeria, Vietnam, and the USSR and frequent our emergency departments know the difference between care available to them in New York City and that in their native countries; even in our municipal hospitals, care is light-years better. But the real problem is not whether these persons have to wait a long time to receive health care, for in the long run they are the lucky ones. The real problem is with those who never show up or who only come when it is too late.

Why do so many people make so many bad decisions? Why has the incidence of measles, a completely preventable disease, skyrocketed? Why will we report in 1990 in New York City over 1,000 cases of congenital syphilis, a disease we learned to treat successfully 40 years ago, while in 1980 we had only 50 cases? Why do we have neighborhoods in New York City, separated by a few dozen blocks, where the infant mortality rate varies fivefold: from 5 to 25 deaths per 1,000 live births—a rate higher than that for Chile, Romania, or Kuwait?

Why is tuberculosis, the leading cause of death in 1890, on the rise once again? This year, the New York City Department of Health will identify 1,000 more cases than we did last year as this disease spreads among the poor and among those who are immunologically compromised, most with HIV disease.

Why do these discrepancies exist? Because in America we have developed a complicated maze that we euphemistically call a health care system. Characteristics of those who can successfully navigate this maze include a college education, a job, third-party insurance coverage, the ability to speak English, and a tendency to stay informed about health through the lay "medical" journals, including *Redbook*, *Reader's Digest*, and *USA Today*, or through the insights offered in the forums presented by Phil, Geraldo, Oprah, and Sally Jesse. But the most important characteristic is a concern about the future, either one's own future or the future of one's children.

Those who cannot make it through the maze have a different set of characteristics. They are disproportionately African American and Latino, they are disproportionately urban, and they use drugs, including tobacco and alcohol, in much higher proportions. They are unemployed or underemployed, and they have no one to call other than 911 when illness strikes.

Why do these discrepancies exist? Because in America today for far too many of us the social infrastructure that most of us take for granted does not exist. Health and medical care are just not the priority for the day. Economic survival is. Or drugs. Or the continued confrontation with despair. There is nothing in stock in any pharmacy to cure those ills.

Not only have we developed a system in which many poor patients cannot, do not, or will not get the care that is easily available to the rest of us, there is increasing evidence that those of us who have access to the miracles of modern medicine get too much care. Some studies suggest that large numbers of patients have had serious medical procedures done without appropriate medical indications. What the patients did have was insurance to cover the procedures.

People with money may be getting too much care that does little good or is harmful, while people without money get too little care that is necessary and beneficial. For example, we have known for years that too many women are subjected to surgical procedures such as hysterectomies, for which the indications are equivocal. Yet we live in a country that cannot and will not answer the question of whether basic primary medical care is a right or whether it remains a privilege for those who can afford it.

I think the most notable advance in this century in medicine was not penicillin, was not dialysis, was not cardiac transplantation, and was not genetically engineered drugs, even though each of these miracles has contributed a great deal to our health as a nation. The most significant advance in medicine occurred in the 1960s, when we still believed we were creating the Great Society and established the Medicare and Medicaid programs. All at once, a generation of disenfranchised Americans, the poor and the elderly, gained access to reasonable health care.

What we need now is a national commitment to the equitable distribution of health care resources throughout the population. On the one hand, we do provide public hospitals, but we fail to invest the appropriate resources to improve their efficiency. We are confused as a nation, for as a public we will pay for the expensive care that an underweight infant will require in the neonatal intensive care unit, but we will not create a system to provide the mother with universal

access to low-cost, effective prenatal care—the kind of care that might have eliminated the need for a costly admission to the intensive care unit.

What America needs is a commitment to correct the many health care wrongs we commit every day. Our crime is that we have chosen to ignore the signs and symptoms of a health care system in disrepair. We are guilty of gross neglect of huge portions of our population whose ability to contribute to our society would be dramatically enhanced by high-quality primary health care. We foolishly ignore all we know to be true about drugs and alcohol and tobacco and guns, and instead we allow political special interests to dominate our legislative bodies. Then we ask physicians in our trauma centers to perform miracles, for we do not yet know how to stop a cocaine overdose in progress or how to cure lung cancer or alcoholic hepatitis; nor can we, in months or years of therapy, undo what a 9-mm hollow-point bullet can do in a fraction of a second.

In 1991, unlike 1891, bacterial infections no longer top the list of our leading preventable causes of death. Today it is ignorance or neglect. We have it within our power to design a social and health care system that works, that provides the right amount of primary health care, the right amount of technology, and one that emphasizes prevention; yet we will not put an appropriate system in place.

If we would take just half of the brain power—half of the energy—that has gone into defense and put it to work designing a rational health care system, we could defeat the enemy of ignorance that now defeats us on a daily basis.

Adapted from the keynote speech given at the Stanford University "You Can Make a Difference" Conference, January 26, 1991, Stanford, California.

WOODROW A. MYERS, Jr, MD, MBA
City Health Commissioner
New York City Department of Health
New York City, New York

Correspondence

The Editors will be pleased to receive and consider for publication correspondence containing information of interest to physicians or commenting on issues of the day. Letters ordinarily should not exceed 600 words and must be typewritten, double-spaced, and submitted in duplicate (the original typescript and one copy). Authors will be given the opportunity to review the editing of their correspondence before publication.

Redwood Medicare Assignment Program

To THE EDITOR: Humboldt County, in northwest California, has developed a successful Medicare assignment program as a completely voluntary cooperative venture among the Humboldt-Del Norte County Medical Society, the Area I Agency on Aging, and the Humboldt Senior Resource Center. This cooperative effort is the key to the program's achievements. The California Medical Association and the California Department of Aging have both endorsed the program.

The goal of the Redwood Medicare Assignment Program is to help Medicare recipients older than 65 obtain affordable medical care. Its principles are

- Voluntary physician participation after careful explanation. Physician involvement rose from 10% before the program's inception to approximately 70% after the first year. It seems to be leveling off at this point.
- Development of income criteria that would not have a "welfare" stigma. The income limits are $25,000 a year for one person and $30,000 for a couple. No income verification is requested.
- Simplicity of the application procedure and ease of establishing eligibility at a physician's office.

After approximately 18 months of operation, only one area of the program remains unsuccessful. About 8,000 Medicare recipients are estimated to qualify. Despite several intense educational campaigns, fewer than 2,000 have actually applied.

For a more detailed description of the program, please write to the Humboldt County Medical Society, PO Box 6457, Eureka, CA 95501.

HERBERT NOTKIN, MD
2612 Hewitt Rd
Arcata, CA 95521

Cancer Patients and Support Groups

To THE EDITOR: We report the results of a recent survey of 292 persons with cancer who were participants in a two-hour-a-week psychosocial support group for an average of 14.5 months at The Wellness Community (TWC). The survey was designed to determine whether people with cancer who participate in support groups abandon conventional medical care. The Wellness Community is a free, nonresidential program, which since opening in Santa Monica in 1982 has provided psychosocial support to over 10,000 persons with cancer.

Our survey was carried out because, despite recent research indicating that psychosocial interventions may have a part to play in the fight against cancer,[1] many physicians still hesitate to endorse such groups, concerned that participation will entice cancer patients to leave traditional medical care.

Over a two-week period during February 1990, a questionnaire was completed by 292 cancer patients, with the following results: Virtually all (287) sought the care of a conventional physician at diagnosis (5 did not answer this question). A total of 274 (93.8%) had been continuously under such care since diagnosis (11 did not answer the question), while 7 left their physicians, 3 because they were in "complete remission," 2 because of personal problems with their physicians, and 1 who had entered alternative treatment.

Thus, most of the 292 respondents had remained under the care of a conventional physician since the time of diagnosis. After approximately 14 months of participation at TWC, only 1 had left conventional care for alternative treatment. We think these findings go beyond the anecdotal in supporting the notion that participation in psychosocial support groups does not impinge upon the use of mainstream medical care.

Our results are, of course, not conclusive, since the cancer patients surveyed were self-selected participants from a single program serving a relatively well-educated, older clientele in one part of the country. Still, they are a start toward a more systematic examination of this question.

HAROLD H. BENJAMIN, PhD
Founder and President
The Wellness Community
2190 Colorado Ave
Santa Monica, CA 90404

MICHAEL S. GOLDSTEIN, PhD
Department of Community Health Sciences
School of Public Health
University of California, Los Angeles
10833 Le Conte Ave
Los Angeles, CA 90024-1772

REFERENCE

1. Spiegel D, Bloom J, Kraemer HC, Gottheil E: Effect of psychosocial treatment on survival of patients with metastatic breast cancer. Lancet 1989; 2:888-891

Lessons From the Practice

The Sailor Who Couldn't Play Pool

PAUL L. KINGSLEY, MD, *Ross, California*

"Sailors are a breed apart." So I was told by the chief medical resident when I reported for duty as an intern at the United States Public Health Service Hospital in July 1953. Little did I know at the time how that statement would influence me adversely in fulfilling my responsibilities to Fred.

Fred, a tall, husky, 40-year-old man of Scandinavian ancestry, had been going to sea for over 12 years, and, like most of the inpatients assigned to me, he sailed on merchant ships. This made him eligible for medical care provided by the Public Health Service.

He told me he had been in port for several weeks and had decided to avail himself of our services while waiting for his next ship. His complaint: "I get a headache when I bend over to play pool."

I asked, "Just when you bend over the pool table to play?"

"Yes."

"Do you get the headache when you bend over to tie your shoes?" I asked.

"No."

"When you bend over for any other reason, do you get the headache?"

"No."

"Have you felt this headache at any time other than when you're bending over a pool table?"

"No, Doctor," Fred said as he smiled. To me, he looked hale and hearty and seemed too relaxed and comfortable to be a patient.

"Just where is this headache located?" I asked.

"Back here," he said as he placed the palm of his right hand at the back of his head.

Baffled, I took a detailed history, only to learn that Fred had no symptoms other than his headache. The results of a thorough physical examination, including the neurologic, were unrevealing, leading me to suspect that Fred was a nonpatient and very skillful in his deception.

It was common knowledge among the hospital staff that some seamen would feign symptoms in order to gain admittance to the hospital. At no cost to them, they were able to obtain not only board and room, but also an ongoing supply of poker players and a chance to chat with buddies they had not seen for months. Of the patients reporting gastrointestinal bleeding, for example, only a small percentage showed any evidence of such bleeding on careful and thorough evaluation. The word had gone out that by simply saying, "I vomited blood," or "I've had some black stools," a seaman could assure himself of a hospital stay of a week or more as he awaited the results of his "workup." And, of course, disorders that were more difficult to evaluate took longer.

On occasion, when I passed by the patients' lounge, I noticed Fred enjoying himself playing poker or visiting with his friends, some old, some new, all the while his ruddy complexion, quick movements, and high spirits belying his inpatient status. The other patients clearly liked him; those of us on the staff who had considerable contact with him were, begrudgingly, beginning to enjoy our association with him.

This was not surprising as I had quickly learned that most of the seamen were likable people, yet, for the most part, "a breed apart." Many seemed odd in one way or another. Perhaps when an American, in prosperous times, chose to make his living at sea, he was making a statement about his personality. It meant being away from family and friends for most of the year; many had no family or long-term relationships. Someone described them as "lonely loners." (Foreign seamen often had no other choice, conditions at home being what they were.)

Puzzled by the lack of findings on the examinations thus far, I consulted with the medical resident on the ward and the chief medical resident.

These two physicians were acquainted with the malingering tactics of some of the seamen. On hearing my presentation, they implied that Fred was malingering by smiling and shrugging their shoulders.

"Tell Fred not to play pool until we can do some more tests," the chief resident advised me. As the hospital had no pool tables, this was his way of acknowledging Fred's one-upmanship.

"What further tests do you have in mind?" I asked. Just about everything had been done including skull films and an electroencephalogram. And he appeared so healthy.

"Our neurology consultant will be in next week, and we'll see what he recommends, perhaps a carotid angiogram."

"Why not do the angiogram before he gets here so that he can look at it when he's here? If it's normal, we could discharge Fred and make a bed available for someone who needs it," I urged.

"Angiograms can cause serious complications. They are not without risk. We should wait for the neurologist's recommendations. Is Fred anxious to leave?"

I shook my head. "No, he doesn't have a ship job lined up, so he's happy to stay."

Fred, with no available pool tables, had no further headaches. The staff, including me, viewed him as a malingerer using the hospital as a free rest and recreation center.

Ten days after Fred had been admitted, he fell out of his chair while playing cards. Unconscious and rigid, he died within minutes.

(Kingsley PL: The sailor who couldn't play pool. West J Med 1991 Jul; 155:87-88)

Dr Kingsley is currently retired from private practice in psychiatry and neurology.
Reprint requests to Paul L. Kingsley, MD, PO Box 588, Ross, CA 94947.

I was horrified at the sight of his contorted body on the floor. Feeling crushed by a sense of enormous guilt, I didn't want to believe what I saw.

Postmortem examination revealed a ruptured aneurysm of the basilar artery of his brain. This had ballooned, probably as a result of a congenital weakness of the arterial wall, and finally burst, snuffing out his life.

I felt humbled and ashamed that I had dismissed Fred as being a malingerer. Even though a clinicopathological conference, held to review Fred's case, determined that the workup had proceeded properly and that waiting for the neurologist's opinion regarding the angiogram had been prudent, I felt less inclined ever again to dismiss a rather bizarre patient history.

Concerned Patient

EDMUND VAN BRUNT, MD, *Berkeley, California*

The tall windows at the end of the intensive care unit corridor look eastward over the city. At midmorning on this late fall Sunday, the light is pale gray. Inside, relative quiet, nurses unhurried, four available beds; eight monitors alive—waves drifting across the screens, each in time to its own drummer. Charts and paperwork in neat array for once. Rounds are over, the house staff scattered.

He appeared about this time, his usual on Sundays, and walked slowly to the nursing station. Tousled gray hair, light jacket, no tie on weekends for this chief of service. There were 20 years of experience and caring behind the facial creases, which deepened briefly as he smiled a good morning to the nurse. He picked up a chart. "Mr Ackerman OK?" She reviewed the night's history—stable; bed-scale weight jibes with measured output; chemistries and vascular dynamics OK; comfortable; a continuing favorable diuresis.

She hesitated. Then, "The patient in 7A is a problem; angry, abusive; he succeeded in effectively alienating the night staff. The attending on call is busy downstairs." He glanced at her. Caring, capable, experienced, not prone to exaggeration. "Perhaps I can look in." He exchanged charts with her, opened the door to 7A. Pneumonia-pseudomonas, underlying lymphoma; some complications, improving and out of the unit soon, home in a few more days; poor long-term prognosis, but now?

He entered the room and moved to the foot of the bed. A tired-looking man appearing older than his 48 years glared at him. A few cryptic remarks at first, then a crescendo of complaints, sketchy, erratic, laced with bitterness and underlying fear. Inadequate staff, nurses too busy, residents too busy, his attending's visits too infrequent, too brief. Tests done too often, results delayed—and, by God, actually missing! Doctors won't or can't answer straightforward questions about his condition and future. A noisy "code blue" down the hall night before last; a too-young technician had to call for assistance after three fruitless attempts to draw a simple blood sample. Too many people listen to his chest, pose the same questions, offer little.

For a long time the gray head listens, alert, observing, features deceptively softened. An occasional murmur of acknowledgment, a raised eyebrow, a brief question, a slow nod. "May I sit?" He moves to the side of the bed, he talks simply and honestly of complex issues—the world of the intensive care unit, technology, the interplay of many persons, the problems of managing heavy information loads, the limits of medical knowledge. The physicians and staff are competent, dedicated; patients improve, mostly, at least for respectable periods; there are many things worthwhile. He rises to leave, smiles, holds out his hand. The patient, visibly calmer, looks at him, hesitates, then extends his own. "Thank you, Doctor." Thirty-five minutes have elapsed.

At the nursing station he opens the chart to the progress notes. Beneath the resident's detailed technical entry of an hour earlier he signs his own: Date, time, and "Patient concerned; some features of depression; reassured." He glances up in time to catch the nurse's expression. "Well . . ." He frowned, then smiled at her. "There's only so much time you can spend in a situation like this. Should it be with the chart or the patient?"

(Van Brunt E: Concerned patient West J Med 1991 Jul; 155:88)

Dr Van Brunt recently retired as Director of the Division of Research, Kaiser Permanente Medical Care Program, Oakland, California.
Reprint requests to Edmund Van Brunt, MD, 131 Tamalpais Rd, Berkeley, CA 94708.

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(Continued from Page 24)

July 29-August 2—**Dynamic Psychotherapy.** University of Colorado School of Medicine at The Given Institute, Aspen. Mon-Fri. Contact: Joann Bauer, (303) 270-5195 or (800) 882-9513.

August 2-4—**Recent Advances in Cancer Therapy.** University of Colorado School of Medicine at The Given Institute, Aspen. Fri-Sun. Contact: Joann Bauer, (303) 270-5195 or (800) 882-9153.

August 4-8—**34th Annual Pediatric Program.** University of Colorado School of Medicine, Children's Hospital, and the Colorado Chapter of the American Academy of Pediatrics at the Given Institute, Aspen. Sun-Thurs. Contact: Bobbi Rubingh, (800) 882-9153 or (303) 270-5196.

August 5-9—**Respiratory Therapy Traineeship Program.** Children's Hospital, Denver. Mon-Fri. Contact: Jeff Griebel, (303) 861-6188.

August 8—**Basic and Advanced Fetal Heart Rate Monitoring.** University of Colorado Health Sciences Center, Denver. Thurs. Contact: Trish Beachy or Nancy Briggs, (303) 270-7117.

August 8-11—**Pulmonary Physiology.** University of Colorado School of Medicine at The Given Institute, Aspen. Thurs-Sun. Contact: Joann Bauer, (303) 270-5195 or (800) 882-9153.

August 15-17—**Musculoskeletal Society Annual Meeting.** In association with University of Colorado School of Medicine at Snowmass. Contact: Joann Bauer, (303) 270-5195 or (800) 882-9153.

August 17-24—**Eleventh Annual Comprehensive Fine Needle Biopsy Course.** University of California, San Francisco, at Aspen's Hotel Jerome. Sat-Sat. Contact: University of California, San Francisco, School of Medicine, Extended Programs in Medical Education, (415) 476-4251.

August 19-23—**Internal Medicine Board Review.** University of Colorado School of Medicine, Denver. Mon-Fri. Contact: Joann Bauer, (303) 270-5195 or (800) 882-9153.

August 25-31—**Primary Care Orthopedics.** University of Colorado School of Medicine at The Given Institute, Aspen. Sun-Sat. Contact: Joann Bauer, (303) 270-5195 or (800) 882-9153.

September 5, 12, 19, 26—**Comprehensive Perinatal Nursing Course.** University of Colorado Health Sciences Center. Thurs. Contact: Trish Beachy or Nancy Briggs, (303) 270-7117.

September 13-14—**Colorado Post-Polio Connection 1991 Education Conference.** Colorado Easter Seal Society for Handicapped Children and Adults, Inc, at Westin Hotel at The Tabor Center, Denver. Fri-Sat. Contact: Alison Kron, (303) 233-1666.

September 27-28—**Montrose Fall Clinics for Physicians.** Montrose Memorial Hospital, Montrose. Fri-Sat. Contact: Kathy Holman, (303) 240-7397.

October 7-11—**Family Practice Review.** University of Colorado School of Medicine, Denver. Mon-Fri. Contact: Joann Bauer, (303) 270-5195 or (800) 882-9153.

October 10-13—**Rural Perinatal Traineeship Program.** Children's Hospital, Denver. Thurs-Sun. Contact: Christine Sievers-Spencer, (303) 861-6413.

October 25-26—**14th Annual Perinatal Conference.** Children's Hospital of Denver at Laramie, Wyoming. Fri-Sat. Contact: Christine Sievers-Spencer, (303) 861-6413.

November 7-10—**Rural Perinatal Traineeship Program.** Children's Hospital, Denver. Thurs-Sun. Contact: Christine Sievers-Spencer, (303) 861-6413.

November 14—**Pre-term Infant Feeding Conference.** University of Colorado Health Sciences Center, Denver. Thurs. Contact: Trish Beachy or Nancy Briggs, (303) 270-7117.

November 22-23—**Colorado Springs Perinatal Conference.** Children's Hospital of Denver at Colorado Springs. Fri-Sat. Contact: Christine Sievers-Spencer, (303) 861-6413.

December 2-6—**Respiratory Therapy Traineeship Program.** Children's Hospital, Denver. Mon-Fri. Contact: Jeff Griebel, (303) 861-6188.

First Wednesday of Each Month—**Various Topics in Neurology.** Sponsored by the Colorado Society of Clinical Neurologists. Contact: Colorado Society of Neurologists, (303) 449-3566.

CONTACT INFORMATION

U of Colo. Contact: University of Colorado School of Medicine, Office of Continuing Medical Education, 4200 E. 9th Ave, Denver, CO (303) 270-5195

IDAHO

July 25-27—**Idaho Medical Association—Annual Meeting.** Sun Valley. Thurs-Sat. Contact: IMA, 305 W Jefferson, PO Box 2668, Boise 83701. (208) 344-7888.

NEW MEXICO

Information, requests for accreditation, and items to be listed should be sent to the chair of the CME Committee, New Mexico Medical Society, 7770 Jefferson, Suite 400, Albuquerque, NM 87109, at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 828-0237.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

July 15-17—**Issues in Primary Pediatric Practice.** Hilton Hotel, Santa Fe. Contact: Susan Hughes, Scott and White Hospital, 2401 S 31st St, Temple, TX 76508. (817) 774-4083.

July 17-20—**Current Concepts in General Surgery.** Hilton Hotel, Albuquerque. Contact: University of New Mexico School of Medicine, Office of CME, PO Box 713, Albuquerque 87131. (505) 277-3942.

July 26-28—**Arrhythmias: Diagnosis and Treatment.** El Dorado Hotel, Santa Fe. Contact: Jan Grieve, New Mexico Heart Clinic, 1001 Coal SE, Albuquerque 87106. (505) 242-2796 or (800) 888-6642.

August 1-3—**Care of the Competitive Athlete: A Team Approach.** Four Seasons Hotel, Albuquerque. Contact: University of New Mexico School of Medicine, Office of CME, PO Box 713, Albuquerque 87131. (505) 277-3942.

August 5-9—**Body Imaging: Ultrasound, CT, MR, Nuclear Medicine.** El Dorado Hotel, Santa Fe. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077. (404) 641-9773.

September 5-7—**Frontiers of Health and Population Research.** Lovelace Medical Foundation, William Randolph Education Building, Albuquerque. Contact: Cathy Barboa, 2441 Ridgecrest SE, Albuquerque 87108. (505) 262-7650.

September 13-14—**New Mexico Chapter, American College of Surgeons—Annual Scientific Meeting.** Ramada Classic Hotel, Albuquerque. Contact: Diane Sansonetti, MD, 201 Cedar SE, Suite 810, Albuquerque 87106, (505) 842-9154, or Bonnie Smith, New Mexico Medical Society, (505) 828-0237 or (800) 748-1596.

September 22-25—**Fourth Annual Southwest Regional Substance Abuse Conference: A Continuum of Care.** Holiday Inn Pyramid, Albuquerque. Contact: Marian Greher, 1479 Morning Glory NE, Albuquerque 87122. (505) 299-2266.

October 12-13—**Common Problems in Pediatric Nephrology.** Cloudcroft Lodge, Cloudcroft. Contact: Joe Dean, MD, 813 N Washington, Roswell 88201. (505) 622-2606.

November 1-3—**The 12 Lead ECG for the Primary Care Physician.** Presbyterian Hospital, Albuquerque. Contact: Jan Grieve, New Mexico Heart Clinic, 1001 Coal SE, Albuquerque 87106. (505) 242-2796 or (800) 888-6642.

November 8—**G.I. Update 1991.** Marriott Hotel, Albuquerque. Contact: Ann Winter, St Joseph Health Care Systems, 601 Grand NE, Albuquerque 87102. (505) 246-8004.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. Accredited institutions wishing to list AMA Category 1 CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, UT 84102; or phone (801) 355-5290. For information on CME accreditation, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution.

(Continued on Page 91)

CONTINUING MEDICAL EDUCATION

(Continued from Page 90)

MEDICAL GRAND ROUNDS

Each Wed—8:00-9:00 a.m. Alternating between University of Utah Medical Center and VA Medical Center, Salt Lake City. Contact: William D. Odell, MD, PhD, Professor and Chairman, Dept of Internal Medicine, Univ of Utah, (801) 581-7606.

* * *

August 1-3—**Utah Ophthalmological Society Annual Shakespearean Festival Meeting** (Sponsor: UOS). Thurs-Sat. Southern Utah State College, Cedar City. Contact: UOS.

September 27-29—**Laser Surgery—Laparoscopic Cholesystectomy** (Sponsor: UUSM). Fri-Sun. The Laser Institute, University of Utah, Salt Lake City. Contact: (801) 581-7001.

November 15-16—**Laser Surgery—Laparoscopic Cholesystectomy** (Sponsor: UUSM). Fri-Sat. The Laser Institute, University of Utah, Salt Lake City. Contact: (801) 581-7001.

SPONSORS OF COURSES—ABBREVIATIONS

AHA:	American Heart Association, Utah Affiliate, 645 E 400 South, Salt Lake City 84102. (801) 322-5601.
CH:	Castleview Hospital (formerly Carbon Hospital), RFD 2, Box 46, Price 84501. (801) 637-4800.
HCH:	Holy Cross Hospital, 1045 E First South, Salt Lake City 84102. (801) 350-4744
ITS:	Intermountain Thoracic Society, 1616 S 11th East, Salt Lake City 84105. (801) 484-4456.
LDSH	LDS Hospital, 8th Ave and "C" St, Salt Lake City 84143. (801) 321-1100.
LRH:	Logan Regional Hospital, 1400 N 5th East, Logan 84321. (801) 752-2050.
MDH:	McKay-Dee Hospital Center, 3939 Harrison Blvd, Ogden 84409. (801) 399-4141.
MVH	Mountain View Hospital, 1000 E Highway 6, Payson 84651. (801) 465-9201.
144:	144th Evacuation Hospital, PO Box 8000, Salt Lake City 84108 (801) 524-3924.
OSS	Ogden Surgical Society, PO Box 9311, Ogden 84409.
PVH:	Pioneer Valley Hospital, 3460 S 4155 West, West Valley City 84120. (801) 968-9061
UOS:	Utah Ophthalmological Society, 540 E 500 South, Salt Lake City 84102. (801) 355-7477.
USH	Utah State Hospital, PO Box 270, Provo 84603-0270. (801) 373-4400
UUSM	University of Utah School of Medicine, Office of Continuing Medical Education, 50 N Medical Dr, Salt Lake City 84132. (801) 581-8664
VAMC:	Veterans Administration Medical Center, 500 Foothill Dr, Salt Lake City 84148. (801) 582-1565
VVMC:	Valley View Medical Center, 595 S 75 East, Cedar City 84720. (801) 586-6587.
WRI:	Western Rehabilitation Institute, 8074 S 1300 East, Sandy 84094 (801) 561-3400.

WASHINGTON

The listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here, please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle, WA 98121; or phone (206) 441-WSMA.

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

July 25-27—**Summer Radiology Meeting.** Coeur d'Alene Resort, Idaho. Thurs-Sat. Contact: Sacred Heart Medical Center, Dept. of Radiology, (509) 455-3352.

July 26-28—**Sealair XII: Regional Anesthesia.** Seattle. Fri-Sun. Contact: VMMC.

August 1-3—**STD Update.** Seattle. Thurs-Sat. Contact. U/W.

(Continued on Page 93)

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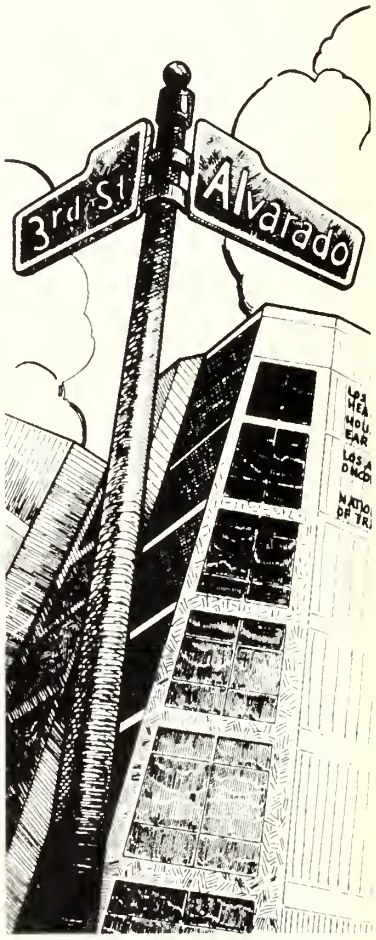

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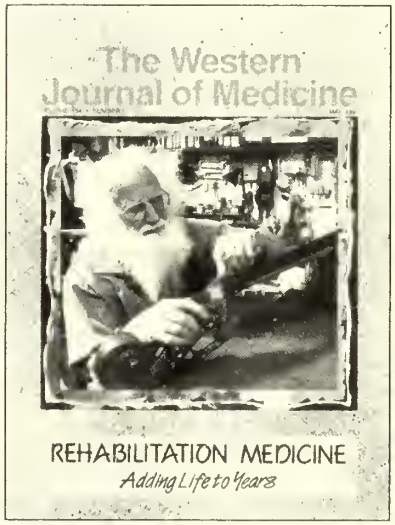

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- Rehabilitation in Rheumatic Diseases *Mary L. Jurisson*
- Rehabilitation of Occupational Low Back Pain *Gerald P. Keane*
- HIV Infection: Implications for Rehabilitation Medicine *Jon A. Mukand*
- Pain Centers: Organization and Outcome *Sridhar V. Vasudevan and N. Timothy Lynch*
- Use It or Lose It: The Hazards of Bed Rest and Inactivity *Paul J. Corcoran*
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CONTINUING MEDICAL EDUCATION

(Continued from Page 91)

August 5-10—**Summer Seminar in Health Care Ethics.** Seattle. Mon-Sat. Contact: U/W.

August 9-11—**International Conference on Pancreatic Cancer.** Seattle. Fri-Sun. Contact: VMMC.

August 15-18—**World Gathering on Bereavement.** Kirkland. Thurs-Sun. Contact: Evergreen Hospital, (206) 878-3710.

August 17-18—**Advanced Cardiac Life Support.** Seattle. Sat-Sun. Contact: VMMC.

August 23-25—**ACCME Regional Workshop.** Seattle. Fri-Sun. Contact: U/W.

September 12-13—**Resolving the Ethical Dilemmas in Animal Protocol Review.** Seattle. Thurs-Fri. Contact: U/W.

September 13—**New Therapies in Hepatobiliary Disease.** Seattle. Fri. Contact: VMMC.

September 16-20—**Family Practice Review.** Seattle. Mon-Fri. Contact: U/W.

September 20-21—**Practical Management of Substance Abuse.** Seattle. Thurs-Fri. Contact: U/W.

September 26—**Cardiology Update.** Everett. Thurs. Contact: Pacific Northwest Medical Education Institute, (206) 258-6322.

September 27—**Surgery Update.** Seattle. Fri. Contact: U/W.

October 5—**2nd Annual Practice Update for Rural Physicians.** Seattle. Sat. Contact: VMMC.

October 10-12—**Burn Update.** Seattle. Thurs-Sat. Contact: U/W.

October 17-19—**Endoscopic Sinus Surgery.** Seattle. Thurs-Sat. Contact: U/W.

October 18—**Atypical Pneumonia Syndromes.** Seattle. Fri. Contact: VMMC.

October 18-20—**Spinal Cord Injury.** Seattle. Fri-Sun. Contact: U/W.

October 24—**Geriatrics.** Everett. Thurs. Contact: Pacific Northwest Medical Education Institute, (206) 258-6322.

November 1—**Radiosurgery Update.** Seattle. Fri. Contact: VMMC.

November 7-8—**Drug Update: Prescription for the '90s.** Seattle. Thurs-Fri. Contact: (206) 258-6322.

November 8—**25th Annual Cancer Conference.** Seattle. Fri. Contact: VMMC.

November 14-15—**Drug Therapy.** Seattle. Thurs-Fri. Contact: U/W.

December 6—**Practical Pediatrics.** Seattle. Fri. Contact: VMMC.

December 6-7—**Urology.** Seattle. Fri-Sat. Contact: (206) 441-9762.

December 12-14—**American College of Physicians.** Seattle. Thurs-Sat. Contact: U/W.

December 12-14—**7th Annual ID Conference.** Everett. Thurs-Sat. Contact: Pacific Northwest Medical Education Institute, (206) 258-6322.

COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Avenue, Seattle, WA 98104. (206) 223-5953.

PCMS CME—Contact: Mrs Maxine Bailey, Executive Director, College of Medical Education, 705 South Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON)—Contact: U/W School of Medicine, Div of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

WSMA—Washington State Medical Association, Continuing Medical Education, 2033 Sixth Ave, Suite 900, Seattle, WA 98121. (206) 441-9762.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, PO Box 900, Seattle, WA 98111. (206) 223-6898.

WYOMING

October 25-26—**14th Annual Perinatal Conference.** Children's Hospital of Denver at Laramie. Fri-Sat. Contact: Christine Sievers-Spencer, (303) 861-6413. ◆

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References:

1. A. Morales et al., New England Journal of Medicine: 1221. November 12, 1981.
2. Goodman, Gilman — The Pharmacological basis of Therapeutics 6th ed., p. 176-188. McMillan December Rev. 1/85.
3. Weekly Urological Clinical letter, 27:2, July 4, 1983.
4. A. Morales et al., The Journal of Urology 128: 45-47, 1982.

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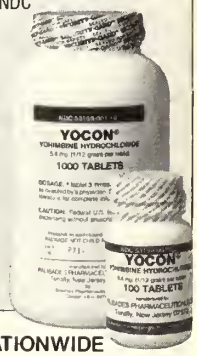

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(Continued on Page 96)

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(Continued from Page 94)

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(Continued on Page 98)

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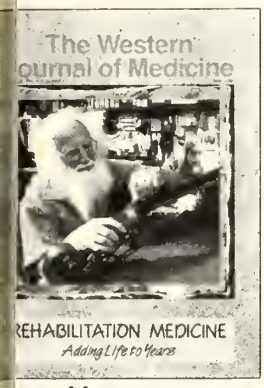

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- PAIN CENTERS: ORGANIZATION AND OUTCOME *Sridhar V. Vasudevan and N. Timathy Lynch*
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- SUBSTANCE ABUSE AND PULMONARY PATHOLOGY *Danald Tashkin*
- SPECIAL POPULATIONS: THE ADOLESCENT *Martha Marrison*
- METHADONE MAINTENANCE IN THE TREATMENT OF OPIOID DEPENDENCE *Jaan Zweben*
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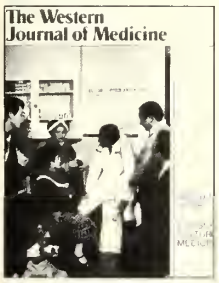

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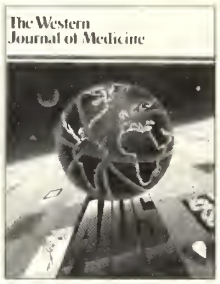

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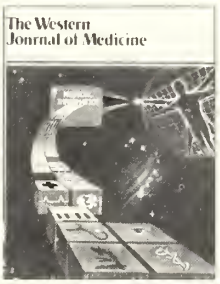

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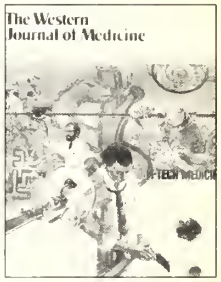

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(Continued on Page 99)

(Continued from Page 98)

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BE/BC INTERNIST sought with or without subspecialty interest to replace departing partner in busy seven member Internal Medicine practice ten miles south of San Francisco. Contact Diane Davis, MD; (415) 583-5352, 1001 Sneath Ln, San Bruno, CA 94066.

MULTIPLE FAMILY PRACTICE (BC/BE) positions available in several suburban satellite clinics of a large Seattle area multispecialty group practice. Diverse patient population includes managed care, fee-for-service, and retired military (at some satellite clinics). Competitive salary and excellent benefits. Contact Mary Anderson, Pacific Medical Center, 1200 12th Ave S., Seattle, WA 98144; (206) 326-4111.

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(Continued on Page 102)

(Continued from Page 101)

PHYSICIAN (FAMILY PRACTICE). Monday through Friday, 40 hours per week, 8-4, $103,056 per year. Will perform comprehensive medical services to include examination, diagnosis, and treatment to outpatients. Such services will include performing a variety of office surgical procedures including sclerotherapy of varicose veins. Will also provide primary ocular care including refraction examinations. Will have administrative responsibilities such as supervision of support staff and making recommendations for improving the quality of medical services provided while reducing the cost for services. Doctorate of Medicine (to include completion of internship and residency) plus two years experience in surgical procedures to include sclerotherapy of varicose veins, and primary ocular care including refraction examination, in a general practice; or Doctorate of Medicine (to include completion of internship and residency) plus two years experience in job offered. Current Arizona state license to practice medicine required. Qualified applicants send résumé or application letter with ad by August 5, 1991 to: Arizona DES Job Service, Attn: 732A Re: Job Order # 5311034, PO Box 6123, Phoenix, AZ 85004. (Job location: Mesa, AZ. Emp Pd Ad. Proof of authorization to work in US required if hired.)

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CALIFORNIA MEDICAL/LEGAL DISABILITY EVALUATIONS opportunities available in San Jose and Fremont, California for BC physicians in Orthopedics, Neurology, Ophthalmology, Otolaryngology, Psychiatry, Toxicology, and Cardiology with multispecialty forensic medical evaluation group. Practice limited to evaluations. Excellent opportunity to supplement income. Send inquiry and CV to Martie Woodson, QME, 39039 Paseo Padre Pkwy, Fremont, CA 94538; (415) 792-7271.

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(Continued on Page 103)

(Continued from Page 102)

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PHYSICIAN—MONDAY THROUGH FRIDAY, 40 hours per week, 8-4, $103,056 per year. Will perform comprehensive medical services to include examination, diagnosis, and treatment of outpatients and will provide acute ambulatory medical care services for emergency situations. Will also treat athletic and orthopedic injuries. Will make recommendations for purchasing medical equipment used for emergency care. Will have administrative duties such as the hiring, firing, and supervision of support staff, and making recommendations for improving the overall quality and efficiency of the acute ambulatory care practice using fiscal management procedures and strategic planning. Doctorate of Medicine (to include completion of internship and residency) plus two years experience working in an acute ambulatory care environment including nonsurgical treatment of athletic and/or orthopedic injuries; or Doctorate of Medicine (to include completion of internship and residency) plus two years experience in job offered. Current Arizona state license to practice medicine required. Qualified applicants send résumé or application letter with ad by August 5, 1991 to: Arizona DES Job Service, Attn: 732A Re: Job Order #5251140, PO Box 6123, Phoenix, AZ 85004. (Job location: Scottsdale, AZ. Emp Pd Ad. Proof of authorization to work in US required if hired.)

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(Continued on Page 104)

(Continued from Page 103)

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Arizona Medical Association, Inc—810 W Bethany Home Rd, Phoenix 85013. (602) 246-8901. Annual Meeting: 1992, date and location to be announced.

California Medical Association—PO Box 7690, San Francisco 94120-7690. (415) 541-0900. Annual Meeting: March 13-18, 1992, Disneyland Hotel, Anaheim.

Colorado Medical Society—PO Box 17550, Denver 80217-0550. (303) 779-5455. Annual Meeting: September 20-22, 1991, Snowmass.

Hawaii Medical Association—1360 S Beretania, Honolulu 96814. (808) 536-7702. Annual Meeting: October 11-13, 1991, Westin Kauai.

Idaho Medical Association—305 W Jefferson, PO Box 2668, Boise 83701. (208) 344-7888. Annual Meeting: July 25-27, 1991, Sun Valley.

Montana Medical Association—2012 11th Ave, Suite 12, Helena 59601. (406) 443-4000. Annual Meeting: October 3-4, 1991, Kalispell.

Nevada State Medical Association—3660 Baker Lane, Reno 89502. (702) 825-6788. Annual Meeting: 1992, date and location to be announced.

New Mexico Medical Society—7770 Jefferson, Suite 400, Albuquerque 87109. (505) 828-0237. Annual Meeting: 1992, date and location to be announced.

Oregon Medical Association—5210 SW Corbett Ave, Portland 97201. (503) 226-1555. Annual Meeting (House of Delegates only): 1992, date and location to be announced.

Utah Medical Association—540 E Fifth South, Salt Lake City 84102. (801) 355-7477. Annual Meeting: September 11-13, 1991, University Park Hotel, Salt Lake City.

Washington State Medical Association—900 United Airlines Bldg, 2033 6th Ave, Seattle 98121. (206) 441-WSMA. Annual Meeting: September 19-22, 1991, Red Lion, Bellevue.

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ADVERTISING INDEX

BLUE CROSS OF CALIFORNIA 19

BLUE SHIELD OF CALIFORNIA 5

BOEHRINGER INGELHEIM PHARMACEUTICALS INC.
Mexitil/Atrovent 11

CIBA-GEIGY PHARMACEUTICALS 13

CIGNA HEALTHPLAN 99

CLASSIFIED ADVERTISING 94, 96, 98, 99, 100, 101, 102, 103, 104

ELI LILLY & COMPANY
Humulin 8, 89

GLAXO PHARMACEUTICALS
Zantac ..... 3rd and 4th covers

KAISER PERMANENTE 101

MARION MERRELL DOW INC.
Cardizem 9, 10
Nicorette 20, 21, 22

PALISADES PHARMACEUTICALS INC.
Yacan 93

PHYSICIANS INTERINDEMNITY INSURANCE 3

ST. VINCENT MEDICAL CENTER 91

SCHERING CORPORATION
Praventil 17

G.D. SEARLE & COMPANY
Calan SR 7

SMITHKLINE BEECHAM PHARMACEUTICALS
Augmentin 25, 26

SUNLIFE OB/GYN SERVICES INC. 101

UPJOHN COMPANY
Rogaine ..... 2nd cover, 1, 23, 24

US AIR FORCE 95

WELLS FARGO BANK 15

THE WESTERN JOURNAL OF MEDICINE
Special Issue—Rehabilitation Medicine 92
Special Issues 97
Subscription 1, 25

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CONTRAINDICATIONS: Zantac® is contraindicated for patients known to have hypersensitivity to the drug.

PRECAUTIONS:

General: 1. Symptomatic response to Zantac® therapy does not preclude the presence of gastric malignancy.
2. Since Zantac is excreted primarily by the kidney, dosage should be adjusted in patients with impaired renal function (see DOSAGE AND ADMINISTRATION). Caution should be observed in patients with hepatic dysfunction since Zantac is metabolized in the liver.

Laboratory Tests: False-positive tests for urine protein with Multistix® may occur during Zantac therapy, and therefore testing with sulfosalicylic acid is recommended.

Drug Interactions: Although Zantac has been reported to bind weakly to cytochrome P-450 *in vitro*, recommended doses of the drug do not inhibit the action of the cytochrome P-450-linked oxygenase enzymes in the liver. However, there have been isolated reports of drug interactions that suggest that Zantac may affect the bioavailability of certain drugs by some mechanism as yet unidentified (eg, a pH-dependent effect on absorption or a change in volume of distribution).

Carcinogenesis, Mutagenesis, Impairment of Fertility: There was no indication of tumorigenic or carcinogenic effects in lifespan studies in mice and rats at doses up to 2,000 mg/kg/d.

Ranitidine was not mutagenic in standard bacterial tests (*Salmonella, Escherichia coli*) for mutagenicity at concentrations up to the maximum recommended for these assays.

In a dominant lethal assay, a single oral dose of 1,000 mg/kg to male rats was without effect on the outcome of two matings per week for the next nine weeks.

Pregnancy: ***Teratogenic Effects: Pregnancy Category B.*** Reproduction studies have been performed in rats and rabbits at doses up to 160 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to Zantac. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: Zantac is secreted in human milk. Caution should be exercised when Zantac is administered to a nursing mother.

Pediatric Use: Safety and effectiveness in children have not been established.

Use in Elderly Patients: Ulcer healing rates in elderly patients (65 to 82 years of age) were no different from those in younger age groups. The incidence rates for adverse events and laboratory abnormalities were also not different from those seen in other age groups.

ADVERSE REACTIONS: The following have been reported as events in clinical trials or in the routine management of patients treated with Zantac®. The relationship to Zantac therapy has been unclear in many cases. Headache, sometimes severe, seems to be related to Zantac administration.

Central Nervous System: Rarely, malaise, dizziness, somnolence, insomnia, and vertigo. Rare cases of reversible mental confusion, agitation, depression, and hallucinations have been reported, predominantly in severely ill elderly patients. Rare cases of reversible blurred vision suggestive of a change in accommodation have been reported.

Cardiovascular: As with other H_2-blockers, rare reports of arrhythmias such as tachycardia, bradycardia, atrioventricular block, and premature ventricular beats.

Gastrointestinal: Constipation, diarrhea, nausea/vomiting, abdominal discomfort/pain, and rare reports of pancreatitis.

Hepatic: In normal volunteers, SGPT values were increased to at least twice the pretreatment levels in 6 of 12 subjects receiving 100 mg qid intravenously for seven days, and in 4 of 24 subjects receiving 50 mg qid intravenously for five days. There have been occasional reports of hepatitis, hepatocellular or hepatocanalicular or mixed, with or without jaundice. In such circumstances, ranitidine should be immediately discontinued. These events are usually reversible, but in exceedingly rare circumstances death has occurred.

Zantac® 150 and 300 (ranitidine hydrochloride) Tablets
Zantac® (ranitidine hydrochloride) Syrup

Musculoskeletal: Rare reports of arthralgias.

Hematologic: Blood count changes (leukopenia, granulocytopenia, thrombocytopenia) have occurred in a few patients. These were usually reversible. Rare cases of agranulocytosis, pancytopenia, sometimes with marrow hypoplasia, and aplastic anemia have been reported.

Endocrine: Controlled studies in animals and man have shown no stimulation of any pituitary hormone by Zantac and no antiandrogenic activity, and cimetidine-induced gynecomastia and impotence in hypersecretory patients have resolved when Zantac has been substituted. However, occasional cases of gynecomastia, impotence, and loss of libido have been reported in male patients receiving Zantac, but the incidence did not differ from that in the general population.

Integumentary: Rash, including rare cases suggestive of mild erythema multiforme, and, rarely, alopecia.

Other: Rare cases of hypersensitivity reactions (eg, bronchospasm, fever, rash, eosinophilia), anaphylaxis, angioneurotic edema, and small increases in serum creatinine.

OVERDOSAGE: Information concerning possible overdosage and its treatment appears in the full prescribing information.

DOSAGE AND ADMINISTRATION: (See complete prescribing information in Zantac® product labeling).

Active Duodenal Ulcer: The current recommended adult oral dosage is 150 mg or 10 ml (2 teaspoonfuls equivalent to 150 mg of ranitidine) twice daily. An alternate dosage of 300 mg or 20 ml (4 teaspoonfuls equivalent to 300 mg of ranitidine) once daily at bedtime can be used for patients in whom dosing convenience is important. The advantages of one treatment regimen compared to the other in a particular patient population have yet to be demonstrated.

Maintenance Therapy: The current recommended adult oral dosage is 150 mg or 10 ml (2 teaspoonfuls equivalent to 150 mg of ranitidine) at bedtime.

Pathological Hypersecretory Conditions (such as Zollinger-Ellison syndrome): The current recommended adult oral dosage is 150 mg or 10 ml (2 teaspoonfuls equivalent to 150 mg of ranitidine) twice a day. In some patients it may be necessary to administer Zantac® 150-mg doses more frequently. Doses should be adjusted to individual patient needs, and should continue as long as clinically indicated. Doses up to 6 g/d have been employed in patients with severe disease.

Benign Gastric Ulcer: The current recommended adult oral dosage is 150 mg or 10 ml (2 teaspoonfuls equivalent to 150 mg of ranitidine) twice a day.

GERD: The current recommended adult oral dosage is 150 mg or 10 ml (2 teaspoonfuls equivalent to 150 mg of ranitidine) twice a day.

Dosage Adjustment for Patients with Impaired Renal Function: On the basis of experience with a group of subjects with severely impaired renal function treated with Zantac, the recommended dosage in patients with a creatinine clearance less than 50 ml/min is 150 mg or 10 ml (2 teaspoonfuls equivalent to 150 mg of ranitidine) every 24 hours. Should the patient's condition require, the frequency of dosing may be increased to every 12 hours or even further with caution. Hemodialysis reduces the level of circulating ranitidine. Ideally, the dosage schedule should be adjusted so that the timing of a scheduled dose coincides with the end of hemodialysis.

HOW SUPPLIED: Zantac® 300 Tablets (ranitidine hydrochloride equivalent to 300 mg of ranitidine) are yellow, capsule-shaped tablets embossed with "ZANTAC 300" on one side and "Glaxo" on the other. They are available in bottles of 30 (NDC 0173-0393-40) tablets and unit dose packs of 100 (NDC 0173-0393-47) tablets.

Zantac® 150 Tablets (ranitidine hydrochloride equivalent to 150 mg of ranitidine) are white tablets embossed with "ZANTAC 150" on one side and "Glaxo" on the other. They are available in bottles of 60 (NDC 0173-0344-42) and 100 (NDC 0173-0344-09) tablets and unit dose packs of 100 (NDC 0173-0344-47) tablets.

Store between 15° and 30° C (59° and 86° F) in a dry place. Protect from light. Replace cap securely after each opening.

Zantac® Syrup, a clear, peppermint-flavored liquid, contains 16.8 mg of ranitidine hydrochloride equivalent to 15 mg of ranitidine per 1 ml in bottles of 16 fluid ounces (one pint) (NDC 0173-0383-54).

Store between 4° and 25° C (39° and 77° F). Dispense in tight, light-resistant containers as defined in the USP/NF.

July 1990

Glaxo Pharmaceuticals
DIVISION OF GLAXO INC.
Research Triangle Park, NC 27709

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Please see Brief Summary of Prescribing Information on adjacent page.

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VOLUME 155 • NUMBER 2 AUGUST 1991

ARTICLES

133 Domestic Violence—Risk Factors and Outcomes
D C BERRIOS and D GRADY

136 The Incidence of *Chlamydia pneumoniae* Lower Respiratory Tract Infections Among University Students in Northern California
D K KATZMAN, A C TIPTON, I F LITT, I M FRIEDMAN, R W EMMONS, and J SCHACHTER

140 Student Perceptions of Mistreatment and Harassment During Medical School—A Survey of Ten United States Schools
D C BALDWIN, Jr, S R DAUGHERTY, and E J ECKENFELS

CONFERENCES AND REVIEWS

146 A Practical Approach to Acid-Base Disorders
Discussant: R J HABER

152 Autocrine Growth Factors and Solid Tumor Malignancy
Moderator: J H WALSH
Discussants: W E KARNES, F CUTTITTA, and A WALKER

164 Hepatitis C Virus—A Review
E TANG

EPITOMES

169 Important Advances in Orthopedics

ALERTS, NOTICES, AND CASE REPORTS

174 Superior Mesenteric Artery Thrombosis Associated With Antiphospholipid Syndrome
M E HAMILTON

176 Metastasis-induced Acute Pancreatitis
S S J HUNG and B ARDALAN

178 Spontaneous Intracranial Hypotension—An Uncommon and Underrecognized Cause of Headache
M B JACOBS and P H WASSERSTEIN

RADIOLOGIC CASE

181 Lung Mass and Hemoptysis in a Patient With Tuberculosis
K PADMANABHAN, S R DHAR, and K YEO

COMMENTARY

183 The Perils of Providing Medical Opinion—A State Medical Association's Experience
H E WILLIAMS and L L RAMSEY

186 Medical Education, Training, and Health Care Services in the Republic of Singapore
C H CHEW

EDITORIALS

189 Understanding Autocrine Growth Regulation

CORRESPONDENCE

191 Abortion 'Gag' Rule • Do We Need Warning Labels on Food?

LESSONS FROM THE PRACTICE

193 Routine Gone Awry
C COPPOLA

OTHER FEATURES

109 In Memoriam

118 Continuing Medical Education Activities in California, Hawaii, and Nevada; Colorado; Idaho; New Mexico; Utah; Washington; Wyoming

130 Subscription Information

194 Poem

195 Instructions for Authors

202 Classified Advertising

212 Western State Medical Associations' Meetings

Detailed Table of Contents: 112, 120, 124

Official Journal of the Alaska State Medical Association, the Arizona Medical Association, the California Medical Association, the Denver Medical Society, the Idaho Medical Association, the Nevada State Medical Association, the New Mexico Medical Society, the Utah Medical Association, the Washington State Medical Association, and the Wyoming Medical Society.

Affiliated Clinical Investigation Societies: the Western Association of Physicians; the Western Society for Clinical Investigation; the Western Section, American Federation for Clinical Research; the Western Society for Pediatric Research; the Western Region, Society for Investigative Dermatology

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Their Blood...

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- In the average smoker (20 to 30 cigarettes a day), physiologic nicotine addiction is reinforced with every cigarette

Peak blood levels produce physiologic satisfaction and reinforcement. Craving occurs when the concentration sinks to a lower level, which the smoker will satisfy with the next cigarette.

On cessation of smoking and initiation of therapy with Nicorette, the patient's nicotine blood levels may be reduced by approximately 50% or more, eliminating the sharp peaks which perpetuate dependence.

And on Their Minds.

- 43% of smokers age 35 and over have tried to quit three times or more
- 80% of efforts are unsuccessful
- Fear of the medical risks of smoking is real, intense, and well-documented

Add Control to Commitment

Enhancing the Comfort Level Adds Control to Commitment

Relief of craving can make a world of difference. When used in conjunction with a program of behavior modification under medical supervision, Nicorette can help provide the committed quitter with:

- Relief of physical craving
- Immediate freedom from worry about carcinogens and carbon monoxide
- Freedom to deal more comfortably with habituation and psychosocial factors

Used properly...

Nicorette®

(nicotine polacrilex)

Relieves Craving...
Reinforces Commitment

Please see the brief summary of prescribing information on the adjacent page.

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BRIEF SUMMARY

Nicorette® (nicotine polacrilex)

CAUTION: Federal law prohibits dispensing without prescription

DESCRIPTION: Each piece of Nicorette contains nicotine polacrilex equivalent to 2 mg nicotine and also contains flavors, glycerin, gum base, sodium bicarbonate, sodium carbonate, and sorbitol

INDICATION AND USAGE: Nicorette is indicated as a temporary aid to the cigarette smoker seeking to give up his or her smoking habit while participating in a behavioral modification program under medical or dental supervision. For further information please see Full Prescribing Information

CONTRAINDICATIONS: Nicorette is contraindicated in non smokers

Nicorette is contraindicated in patients during the immediate post myocardial infarction period, patients with life-threatening arrhythmias, and patients with severe or worsening angina pectoris. (See WARNINGS.)

Also, Nicorette is contraindicated in patients with active temporomandibular joint disease.

Current medical opinion indicates that nicotine in any form may be harmful to an unborn child. Nicorette and cigarettes both contain nicotine

Nicorette may cause fetal harm when administered to a pregnant woman

Use of cigarettes or Nicorette during the last trimester has been associated with a decrease in fetal breathing movements. These effects may be the result of decreased placental perfusion caused by nicotine. Rare reports of miscarriages have been received, and a relationship to drug therapy as a contributing factor cannot be excluded. Studies in pregnant rhesus monkeys have shown that maternal nicotine administration produced acidosis, hypoxia and hypercarbia in the fetus

Nicotine has been shown to be teratogenic in mice treated subcutaneously with 25 mg/kg, which is approximately 300 times the human buccal dose. Studies in rats and monkeys have not demonstrated a teratogenic effect of nicotine in doses which would occur during cigarette smoking

Nicorette is therefore contraindicated in women who are or may become pregnant, and female patients should be advised to take adequate precautions to avoid becoming pregnant. The physician may wish to consider a pregnancy test before instituting therapy with Nicorette. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus

WARNINGS: The risks of nicotine in patients with certain cardiovascular and endocrine diseases should be carefully weighed against the benefits of including Nicorette in a smoking cessation program in these patients. Specifically, patients with coronary heart disease (history of myocardial infarction and/or angina pectoris), serious cardiac arrhythmias, or vasospastic diseases (Buerger's disease, Prinzmetal variant angina) should be carefully screened and evaluated before Nicorette is prescribed. Occasional reports of tachyarrhythmias occurring in association with the use of Nicorette have been reported, therefore, if an increase in cardiovascular symptoms occurs with the use of Nicorette, it should be discontinued

As the action of nicotine on the adrenal medulla (release of catecholamines) does not appear to be affected by tolerance, Nicorette should be used with caution in patients with hyperthyroidism, pheochromocytoma or insulin-dependent diabetes

Cigarette smoking is felt to play a perpetuating role in hypertension and peptic ulcer disease. Therefore, Nicorette should be used in patients with systemic hypertension or peptic ulcer (active or inactive) only when the benefits of including Nicorette in a smoking cessation program outweigh the risks

PRECAUTIONS: Nicorette should be used with caution in patients with oral or pharyngeal inflammation and in patients with a history of esophagitis or peptic ulcer

The dosage form of Nicorette dictates that it be used with caution in patients whose dental problems might be exacerbated by chewing gum. In such patients prior dental evaluation may be advisable

Nicorette is sugar-free and has been formulated to minimize stickiness. As with other gums, however, the degree to which Nicorette may stick to dentures, dental caps or partial bridges may depend on the materials from which they are made and other factors such as amount of saliva produced, possible interaction with denture adhesives, denture cleaning compounds, dryness of mouth due to other causes and salivary constituents. Should an excessive degree of stickiness to dental work occur there is a possibility that as with other gums, Nicorette may damage dental work. If this should occur, the patient should discontinue its use and consult a physician or dentist

The sustained use of Nicorette by ex-smokers is not to be encouraged because the chronic consumption of nicotine is toxic and addicting. The physician must, however, weigh the relative risks of a possible return to smoking versus continued, long-term use of the gum

Information for Patients: The patient instruction sheet is attached at the end of the professional labeling text. It is intended for detachment by the pharmacist and inclusion in the package of Nicorette dispensed to the patient. It contains important selected information on patient selection, risks and adverse effects and instructions on how to use Nicorette properly

Drug Interactions: Smoking cessation, with or without nicotine substitutes, may alter response to concomitant medication in ex-smokers. Smoking is considered to increase metabolism and thus lower blood levels of drugs such as phenacetin, caffeine, theophylline, imipramine and pentazocine through enzyme induction. Cessation of smoking may result in increased levels of these drugs. Absorption of glutethimide may be decreased, and the "first pass" metabolism of propoxyphene may be decreased by smoking cessation. Other reported effects of smoking, which do not involve enzyme induction, include reduced diuretic effects of furosemide and decreased cardiac output and increased blood pressure with propranolol, which may also relate to the hormonal effects of nicotine. Smoking cessation may reverse these actions

Both smoking and nicotine can increase circulating cortisol and catecholamines. Therapy with adrenergic agonists or with adrenergic blockers may need to be adjusted according to changes in nicotine therapy or smoking status

Carcinogenesis, Mutagenesis, Impairment of Fertility: Nicotine was not mutagenic in the Ames *Salmonella* test

Literature reports indicate that nicotine is neither an initiator nor a tumor-promoter in mice. There is inconclusive evidence to suggest that cotinine, an oxidized metabolite of nicotine, may be carcinogenic in rats. Cotinine was not mutagenic in the Ames *Salmonella* test

Studies have shown a decrease of litter size in rats treated with nicotine during the time of fertilization

Pregnancy: Pregnancy Category X. (See CONTRAINDICATIONS.)

Nursing Mothers: Nicotine passes freely into the breast milk. Because of the potential for serious adverse reactions in nursing infants from nicotine, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother

Pediatric Use: Safety and effectiveness in children and adolescents who smoke have not been evaluated

ADVERSE REACTIONS: Adverse reactions reported in association with the use of Nicorette include both local effects and systemic effects representing the pharmacologic action of nicotine. Rare reports of an apparent severe allergic reaction have been received

Local side effects: Mechanical effects of gum chewing include traumatic injury to oral mucosa or teeth, jaw ache, and eructation secondary to air swallowing. These side effects may be minimized by modifying chewing technique. Oral mucosal changes such as stomatitis, glossitis, gingivitis, pharyngitis, and aphthous ulcers, in addition to changes in taste perception, can occur during smoking cessation efforts with or without the use of Nicorette

Systemic side effects: Although the systemic effects seen in trials were generally similar, the reported frequency of adverse drug effects was highly variable, as illustrated by the variation observed in adverse event incidences estimated from the results of two well controlled studies (one performed in the United States, and the other in England) designed to evaluate the safety and efficacy of Nicorette. (See table, below.) Given this variability, the table can be used only as an indication of the relative frequency of adverse events reported in representative clinical trials. It can not predict expected incidences of these effects during the course of usual medical practice

Treatment Emergent
Symptom Incidence for the 2 mg Gum

	US		British	
	Drug	Placebo	Drug	Placebo
Number of Subjects Reporting	94	95	58	58
Percent of Subjects Reporting				
Autonomic				
Excess Salivation	2.1	0.0		
CNS				
Insomnia	1.1	1.1		
Dizziness/Light-headedness	2.1	2.1	19.0	13.8
Irritable/Fussy	1.1	1.1		
Headache	1.1	5.3	24.1	29.3
Gastrointestinal				
Nonspecific GI Distress	9.6	6.3		
Eructation	6.4	1.1		
Indigestion			41.4	20.7
Nausea/Vomiting	18.1	4.2	31.0	15.5
Reactions Referable to Mouth, Throat, Jaw or Teeth				
Mouth or Throat Soreness	37.2	31.6	56.9	53.4
Jaw Muscle Ache	18.1	9.5	44.8	44.8
Others				
Anorexia	1.1	1.1		
Hiccups	14.9	0.0	22.4	3.4

The only potentially serious systemic adverse effect observed among the 152 patients evaluated in the controlled clinical trials used to support the efficacy of Nicorette was cardiac irritability: a patient displayed what may have been nicotine-induced, but reversible, atrial fibrillation. Cardiac irritability is a well known consequence of cigarette smoking

A 46-year-old male patient participating in a clinical trial of Nicorette was reported to have developed nicotine intoxication requiring his hospitalization. After 4 days, he was discharged, fully recovered. He died suddenly one month later. Nicorette was not used during this one-month interval. The relationship of the patient's death to his prior treatment is undetermined

Since the marketing of Nicorette in the U.S., reports of several other deaths and reports including myocardial infarction, congestive heart failure, cerebrovascular accident and cardiac arrest have been received. A cause and effect relationship between these reports and the use of Nicorette has not been established

In addition to the reported effects listed above, the following events have been reported: *CARDIOVASCULAR*—edema, flushing, hypertension, palpitations, tachyarrhythmias, tachycardia; *CNS*—confusion, convulsions, depression, euphoria, numbness, paresthesia, syncope, tinnitus, weakness; *DERMATOLOGIC*—erythema, itching, rash, urticaria; *GASTROINTESTINAL*—alteration of liver function tests, constipation, diarrhea; *RESPIRATORY*—breathing difficulty, cough, hoarseness, sneezing, wheezing; *OTHER*—dry mouth, systemic nicotine intoxication

Rare reports of miscarriages have been received, and a relationship to drug therapy as a contributing factor cannot be excluded

DRUG ABUSE AND DEPENDENCE/OVERDOSE/TREATMENT OF OVERDOSAGE: For further information, please see full prescribing information

DOSAGE AND ADMINISTRATION: Most patients require approximately 10 to 12 pieces of gum per day during the first month of treatment. Patients should be instructed not to exceed 30 Nicorette pieces per day. Patients should be assessed after one month of treatment to determine smoking status, and the use of Nicorette as an adjunct should be reevaluated. Gradual withdrawal from Nicorette should be initiated after 3 months' usage and completed by 6 months. The use of Nicorette beyond 6 months' is not recommended

Product Information as of May 1989

Manufactured by Aktiebolaget Leo, Helsingborg, Sweden for
MARION MERRELL DOW INC
Prescription Products Division
Kansas City, MO 64114

NICAE 703/0202 6320HI

YOCON®
YOHIMBINE HCl

Description: Yohimbine is a 3a-15a-20B-17a-hydroxy Yohimbine-16a-carboxylic acid methyl ester. The alkaloid is found in Rubaceae and related trees. Also in Rauwolfia Serpentina (L) Benth. Yohimbine is an indolalkylamine alkaloid with chemical similarity to reserpine. It is a crystalline powder, odorless. Each compressed tablet contains (1/12 gr.) 5.4 mg of Yohimbine Hydrochloride.

Action: Yohimbine blocks presynaptic alpha-2 adrenergic receptors. Its action on peripheral blood vessels resembles that of reserpine, though it is weaker and of short duration. Yohimbine's peripheral autonomic nervous system effect is to increase parasympathetic (cholinergic) and decrease sympathetic (adrenergic) activity. It is to be noted that in male sexual performance, erection is linked to cholinergic activity and to alpha-2 adrenergic blockade which may theoretically result in increased penile inflow, decreased penile outflow or both.

Yohimbine exerts a stimulating action on the mood and may increase anxiety. Such actions have not been adequately studied or related to dosage although they appear to require high doses of the drug. Yohimbine has a mild anti-diuretic action, probably via stimulation of hypothalmic centers and release of posterior pituitary hormone

Reportedly, Yohimbine exerts no significant influence on cardiac stimulation and other effects mediated by B-adrenergic receptors, its effect on blood pressure, if any, would be to lower it; however no adequate studies are at hand to quantitate this effect in terms of Yohimbine dosage.

Indications: Yocon® is indicated as a sympathicolytic and mydriatric. It may have activity as an aphrodisiac.

Contraindications: Renal diseases, and patient's sensitive to the drug. In view of the limited and inadequate information at hand, no precise tabulation can be offered of additional contraindications.

Warning: Generally, this drug is not proposed for use in females and certainly must not be used during pregnancy. Neither is this drug proposed for use in pediatric, geriatric or cardio-renal patients with gastric or duodenal ulcer history. Nor should it be used in conjunction with mood-modifying drugs such as antidepressants, or in psychiatric patients in general.

Adverse Reactions: Yohimbine readily penetrates the (CNS) and produces a complex pattern of responses in lower doses than required to produce peripheral a-adrenergic blockade. These include, anti-diuresis, a general picture of central excitation including elevation of blood pressure and heart rate, increased motor activity, irritability and tremor. Sweating, nausea and vomiting are common after parenteral administration of the drug.[1,2] Also dizziness, headache, skin flushing reported when used orally.[1,3]

Dosage and Administration: Experimental dosage reported in treatment of erectile impotence.[1,3,4] 1 tablet (5.4 mg) 3 times a day, to adult males taken orally. Occasional side effects reported with this dosage are nausea, dizziness or nervousness. In the event of side effects dosage to be reduced to ½ tablet 3 times a day, followed by gradual increases to 1 tablet 3 times a day. Reported therapy not more than 10 weeks.[3]

How Supplied: Oral tablets of Yocon® 1/12 gr. 5.4 mg in bottles of 100's NDC 53159-001-01 and 1000's NDC 53159-001-10.

References:

1. A. Morales et al., New England Journal of Medicine: 1221. November 12, 1981.
2. Goodman, Gilman — The Pharmacological basis of Therapeutics 6th ed., p. 176-188. McMillan December Rev. 1/85.
3. Weekly Urological Clinical letter, 27:2, July 4, 1983.
4. A. Morales et al., The Journal of Urology 128: 45-47, 1982.

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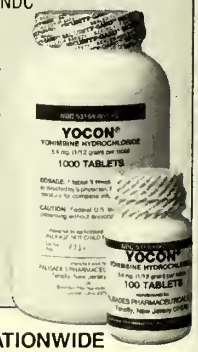

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In Memoriam

California Medical Association

Baker, Stephen T., San Francisco. Died May 19, 1991, aged 46. Graduate of Yale University School of Medicine, New Haven, Connecticut, 1973. Licensed in California in 1981. Dr Baker was a member of the San Francisco Medical Society.

Banta, Edwin, Jr, Redlands. Died Apr 3, 1991, aged 69. Graduate of University of Michigan Medical School, Ann Arbor, 1945. Licensed in California in 1953. Dr Banta was a member of the San Bernardino County Medical Society.

Blaufuss, Arnold, Fresno. Died May 5, 1991, aged 49. Graduate of Tulane University School of Medicine, New Orleans, Louisiana, 1968. Dr Blaufuss was a member of the Fresno-Madera Medical Society.

Borkovic, Steven P., Napa. Died Mar 27, 1991, aged 38. Graduate of Brown University School of Medicine, Providence, Rhode Island, 1979. Licensed in California in 1981. Dr Borkovic was a member of the Napa County Medical Society.

Bramham, James C., Sacramento. Died Mar 17, 1991, aged 68. Graduate of University of California, San Francisco, 1948. Licensed in California in 1948. Dr Bramham was a member of the Sacramento-El Dorado Medical Society.

Cable, Sheldon, San Francisco. Died Mar 20, 1991, aged 56. Graduate of University of Minnesota Medical School, Minneapolis, 1958. Licensed in California in 1959. Dr Cable was a member of the San Francisco Medical Society.

Campion, Gwendolyn, Kentfield. Died May 9, 1991. Graduate of University of Toronto, 1933. Licensed in California in 1936. Dr Campion was a member of the Marin Medical Society.

Cronenwett, Paul H., Alameda. Died Apr 25, 1991, aged 81. Graduate of Stanford University, Stanford, California, 1936. Dr Cronenwett was a member of the Alameda-Contra Costa Medical Association.

Dakin, Richard L., Greenbrae. Died Mar 3, 1991, aged 62. Graduate of Washington University, 1955. Dr Dakin was a member of the Marin Medical Society.

Drapkin, Harold. Died Apr 30, 1991, aged 65. Graduate of University of California, Irvine, 1962. Licensed in California in 1975. Dr Drapkin was a member of the Los Angeles County Medical Association.

Fitch, William M., Bellflower. Died Mar 9, 1991, aged 69. Graduate of University of Nebraska College of Medicine, Omaha, 1948. Licensed in California in 1953. Dr Fitch was a member of the Los Angeles County Medical Association.

Giberson, A. F., Watsonville. Died May 5, 1991, aged 87. Graduate of Stanford University, Stanford, California, 1933. Dr Giberson was a member of the Santa Cruz County Medical Society.

Gibson, George C., Vallejo. Died Apr 18, 1991, aged 77. Graduate of Harvard Medical School, Boston, Massachusetts, 1943. Dr Gibson was a member of the Solano County Medical Society.

Ginsberg, Robert L., Mountain View. Died May 22, 1991, aged 68. Graduate of University of Minnesota, Minneapolis, 1947. Licensed in California in 1948. Dr Ginsberg was a member of the Santa Clara County Medical Association.

Gray, Richard, Berkeley. Died Apr 28, 1991, aged 75. Graduate of Stanford University, Stanford, California, 1945. Dr Gray was a member of the Alameda-Contra Costa Medical Association.

Hamilton, James J., Yuba City. Died Apr 11, 1991, aged 77. Graduate of University of Tennessee Medical School, Memphis, 1940. Dr Hamilton was a member of the Yuba-Sutter-Colusa County Medical Society.

Hanigan, Thomas E., Garden Grove. Died Apr 1991, aged 76. Graduate of University of Colorado, Denver, 1940. Dr Hanigan was a member of the Orange County Medical Association.

Haskins, George W., Riverside. Died Feb 19, 1991, aged 67. Graduate of Northwestern University Medical School, Chicago, Illinois, 1948. Licensed in California in 1953. Dr Haskins was a member of the Riverside County Medical Association.

Hastings, Orville L., Long Beach. Died Jan 30, 1991, aged 79. Graduate of University of California, Irvine, 1962. Licensed in California in 1975. Dr Hastings was a member of the Los Angeles County Medical Association.

Huffer, Richard L., Indio. Died May 18, 1991, aged 62. Graduate of Indiana University School of Medicine, Indianapolis, 1953. Licensed in California in 1957. Dr Huffer was a member of the Riverside County Medical Association.

Humber, John Davis, Calistoga. Died May 20, 1991, aged 95. Graduate of Tulane University School of Medicine, New Orleans, Louisiana, 1920. Dr Humber was a member of the Napa County Medical Society.

Jules, Philip. Died Mar 28, 1991, aged 70. Graduate of Loyola University, Maywood, Illinois, 1949. Licensed in California in 1950. Dr Jules was a member of the Los Angeles County Medical Association.

Klein, Russell R., Sausalito. Died Apr 1, 1991, aged 80. Graduate of Stanford University, Stanford, California, 1932. Dr Klein was a member of the Marin Medical Society.

Lane, Robert D., San Jose. Died May 15, 1991, aged 83. Graduate of Creighton University School of Medicine, Omaha, Nebraska, 1938. Dr Lane was a member of the Santa Clara County Medical Association.

Leonard, Carl D., San Jose. Died May 24, 1991, aged 84. Graduate of University of Kansas Medical School, Kansas City, 1935. Dr Leonard was a member of the Santa Clara County Medical Association.

Lewis, William B., Jr, Riverside. Died Mar 14, 1991, aged 74. Graduate of University of Colorado, Denver, 1943. Licensed in California in 1953. Dr Lewis was a member of the Riverside County Medical Association.

McPharlin, James H., Salinas. Died Apr 20, 1991, aged 87. Graduate of Creighton University, Omaha, Nebraska, 1929. Dr McPharlin was a member of the Monterey County Medical Society.

(Continued on Page 117)

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CONTENTS

ARTICLES

133 **Domestic Violence—Risk Factors and Outcomes**

DANIEL C. BERRIOS, MD, MPH, and DEBORAH GRADY, MD, MPH

From the Department of Epidemiology and Biostatistics, University of California, San Francisco, School of Medicine.

136 **The Incidence of *Chlamydia pneumoniae* Lower Respiratory Tract Infections Among University Students in Northern California**

DEBRA K. KATZMAN, MD; ANN C. TIPTON, MD; IRIS F. LITT, MD; IRA M. FRIEDMAN, MD; RICHARD W. EMMONS, MD, PhD; and JULIUS SCHACHTER, PhD

From the Department of Pediatrics, Division of Adolescent Medicine, Stanford University School of Medicine and Children's Hospital at Stanford, Stanford, California; Departments of Pediatrics, Epidemiology and Biostatistics, and Laboratory Medicine, University of California, San Francisco, School of Medicine; and the Viral and Rickettsial Disease Laboratory, Division of Laboratories, California Department of Health Services, Berkeley.

140 **Student Perceptions of Mistreatment and Harassment During Medical School—A Survey of Ten United States Schools**

DE WITT C. BALDWIN, Jr, MD; STEVEN R. DAUGHERTY, PhD; and EDWARD J. ECKENFELS

From the Division of Medical Education Research and Information, American Medical Association, and Program Evaluation and Academic Counseling, Rush Medical College of Rush University, Chicago, Illinois.

CONFERENCES AND REVIEWS

146 **A Practical Approach to Acid-Base Disorders**

Discussant: RICHARD J. HABER, MD

A discussion selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from a transcription, it was edited by Homer A. Baushey, MD, Professor of Medicine, and Nathan M. Bass, MD, PhD, Associate Professor of Medicine, under the direction of Lloyd H. Smith, Jr, MD, Professor of Medicine and Associate Dean in the School of Medicine.

152 **Autocrine Growth Factors and Solid Tumor Malignancy**

Moderator: JOHN H. WALSH, MD
Discussants: WILLIAM E. KARNES, MD; FRANK CUTTITTA, PhD; and AMEAE WALKER, PhD

An edited summary of an Interdepartmental Conference arranged by the Department of Medicine of the University of California, Los Angeles, School of Medicine. The Director of Conferences is William M. Pardridge, MD, Professor of Medicine.

164 **Hepatitis C Virus—A Review**

EDDIE TANG, MD

From the University of Southern California School of Medicine, Los Angeles. This paper was chosen as the winner of The Western Journal of Medicine's *1991 Medical Student Writing Competition.*

EPITOMES—IMPORTANT ADVANCES IN CLINICAL MEDICINE

Orthopedics

Items of progress in orthopedics. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance.

169 **Tissue Banking**

JUAN J. RODRIGO, MD

(Continued on Page 120)

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For Brief Summary, please see following page.

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References: 1. Newton RE, *et al* A review of the side effect profile of buspirone *Am J Med* 1986,80(3B) 17-21 2. Luckhi, *et al* Differential effects of the anxiolytic drugs, diazepam and buspirone, on memory function *Br J Clin Pharmacol* 1987:23 207-211 3. Lader M Assessing the potential for buspirone dependence or abuse and effects of its withdrawal *Am J Med* 1987,82(5A) 20-26

Contraindications: Hypersensitivity to buspirone hydrochloride.

Warnings: The administration of BuSpar to a patient taking a monoamine oxidase inhibitor (MAOI) may pose a hazard. Since blood pressure has become elevated when BuSpar was administered concomitantly with an MAOI, such concomitant use is not recommended BuSpar should not be employed in lieu of appropriate antipsychotic treatment

Precautions: ***General***—*Interference with cognitive and motor performance:* Although buspirone is less sedating than other anxiolytics and does not produce significant functional impairment, its CNS effects in a given patient may not be predictable; therefore, patients should be cautioned about operating an automobile or using complex machinery until they are reasonably certain that buspirone does not affect them adversely Although buspirone has not been shown to increase alcohol-induced impairment in motor and mental performance, it is prudent to avoid concomitant use with alcohol.

Potential for withdrawal reactions in sedative/hypnotic/anxiolytic drug dependent patients: Because buspirone will not block the withdrawal syndrome often seen with cessation of therapy with benzodiazepines and other common sedative/hypnotic drugs, before starting buspirone withdraw patients gradually from their prior treatment, especially those who used a CNS depressant chronically Rebound or withdrawal symptoms may occur over varying time periods, depending in part on the type of drug and its elimination half-life The withdrawal syndrome can appear as any combination of irritability, anxiety, agitation, insomnia, tremor, abdominal cramps, muscle cramps, vomiting, sweating, flu-like symptoms without fever, and occasionally, even as seizures

Possible concerns related to buspirone's binding to dopamine receptors: Because buspirone can bind to central dopamine receptors, a question has been raised about its potential to cause acute and chronic changes in dopamine mediated neurological function (eg, dystonia, pseudoparkinsonism, akathisia, and tardive dyskinesia) Clinical experience in controlled trials has failed to identify any significant neuroleptic-like activity, however, a syndrome of restlessness, appearing shortly after initiation of treatment, has been reported, the syndrome may be due to increased central noradrenergic activity or may be attributable to dopaminergic effects (ie, represent akathisia)

Information for Patients—Patients should be instructed to inform their physician about any medications, prescription or nonprescription, alcohol or drugs they are now taking or plan to take during treatment with buspirone, to inform their physician if they are pregnant, are planning to become pregnant, or become pregnant while taking buspirone, to inform their physician if they are breast feeding; and not to drive a car or operate potentially dangerous machinery until they experience how this medication affects them.

Drug Interactions—Concomitant use with other CNS active drugs should be approached with caution (see **Warnings**) Concomitant use with trazodone may have caused 3- to 6-fold elevations on SGPT (ALT) in a few patients Concomitant administration of BuSpar and haloperidol resulted in increased serum haloperidol concentrations in normal volunteers. The clinical significance is not clear. Buspirone does not displace tightly bound drugs like phenytoin, propranolol, and warfarin from serum proteins, but may displace less firmly bound drugs like digoxin However, there was one report of prolonged prothrombin time when buspirone was given to a patient also treated with warfarin, phenytoin, phenobarbital, digoxin, and Synthroid

Carcinogenesis, Mutagenesis, Impairment of Fertility—No evidence of carcinogenic potential was observed in rats or mice, buspirone did not induce point mutations, nor was DNA damage observed, chromosomal aberrations or abnormalities did not occur

Pregnancy: Teratogenic Effects—Pregnancy Category B Should be used during pregnancy only if clearly needed

Nursing Mothers—Administration to nursing women should be avoided if clinically possible

Pediatric Use—The safety and effectiveness have not been determined in individuals below 18 years of age

Use in the Elderly—No unusual, adverse, age-related phenomena have been identified in elderly patients receiving a total, modal daily dose of 15 mg

Use in Patients with Impaired Hepatic or Renal Function—Since buspirone is metabolized by the liver and excreted by the kidneys, it is not recommended in severe hepatic or renal impairment

Adverse Reactions (See also Precautions): ***Commonly Observed***—The more commonly observed untoward events, not seen at an equivalent incidence in placebo-treated patients, include dizziness, nausea, headache, nervousness, lightheadedness, and excitement

Associated with Discontinuation of Treatment—The more common events causing discontinuation included central nervous system disturbances (3 4%), primarily dizziness, insomnia, nervousness, drowsiness, lightheaded feeling, gastrointestinal disturbances (1.2%), primarily nausea, miscellaneous disturbances (1 1%), primarily headache and fatigue In addition, 3 4% of patients had multiple complaints, none of which could be characterized as primary

Incidence in Controlled Clinical Trials—Adverse events reported by 1% or more of 477 patients who received buspirone in four-week, controlled trials. *Cardiovascular* Tachycardia/palpitations 1% *CNS* Dizziness 12%, drowsiness 10%, nervousness 5%, insomnia 3%, lightheadedness 3%, decreased concentration 2%, excitement 2%, anger/hostility 2%, confusion 2%, depression 2% *EENT* Blurred vision 2%. *Gastrointestinal* Nausea 8%, dry mouth 3%, abdominal/gastric distress 2%, diarrhea 2%, constipation 1%, vomiting 1% *Musculoskeletal* Musculoskeletal aches/pains 1% *Neurological* Numbness 2%, paresthesia 1%, incoordination 1%, tremor 1% *Skin* Skin rash 1%. *Miscellaneous* Headache 6%, fatigue 4%, weakness 2%, sweating/clamminess 1%

Other Events Observed During the Entire Premarketing Evaluation—The relative frequency of all other undesirable events reasonably associated with the use of buspirone in approximately 3000 subjects who took multiple doses of the drug under well-controlled, open, and uncontrolled conditions is defined as follows Frequent are those occurring in at least 1/100 patients, infrequent are those occurring in 1/100 to 1/1000 patients, and rare are those occurring in less than 1/1000 patients *Cardiovascular*—frequent nonspecific chest pain, infrequent syncope, hypotension, hypertension; rare cerebrovascular accident, congestive heart failure, myocardial infarction, cardiomyopathy, bradycardia *Central Nervous System*—frequent dream disturbances; infrequent depersonalization, dysphoria, noise intolerance, euphoria, akathisia, tearfulness, loss of interest, dissociative reaction, hallucinations, suicidal ideation, seizures; rare feelings of claustrophobia, cold intolerance, stupor, slurred speech, psychosis *EENT*—frequent tinnitus, sore throat, nasal congestion, infrequent redness and itching of the eyes, altered taste, altered smell, conjunctivitis; rare inner ear abnormality, eye pain, photophobia, pressure on eyes. *Endocrine*—rare galactorrhea, thyroid abnormality *Gastrointestinal*—infrequent flatulence, anorexia, increased appetite, salivation, irritable colon, rectal bleeding, rare burning of the tongue *Genitourinary*—infrequent urinary frequency, urinary hesitancy, menstrual irregularity and spotting, dysuria, rare amenorrhea, pelvic inflammatory disease, enuresis, nocturia *Musculoskeletal*—infrequent muscle cramps, muscle spasms, rigid/stiff muscles, arthralgias. *Neurological*—infrequent involuntary movements, slowed reaction time, rare muscle weakness *Respiratory*—infrequent hyperventilation, shortness of breath, chest congestion; rare epistaxis *Sexual Function*—infrequent decreased or increased libido; rare delayed ejaculation, impotence *Skin*—infrequent edema, pruritus, flushing, easy bruising, hair loss, dry skin, facial edema, blisters, rare acne, thinning of nails *Clinical Laboratory*—infrequent increases in hepatic aminotransferases (SGOT, SGPT), rare eosinophilia, leukopenia, thrombocytopenia *Miscellaneous*—infrequent weight gain, fever, roaring sensation in the head, weight loss, malaise, rare alcohol abuse, bleeding disturbance, loss of voice, hiccoughs

Postintroduction Clinical Experience—Rare occurrences of allergic reactions, cogwheel rigidity, dystonic reactions, ecchymosis, emotional lability, tunnel vision, and urinary retention have been reported Because of the uncontrolled nature of these spontaneous reports, a causal relationship to BuSpar has not been determined

Drug Abuse and Dependence: ***Controlled Substance Class***—Not a controlled substance

Physical and Psychological Dependence—Buspirone has shown no potential for abuse or diversion and there is no evidence that it causes tolerance, or either physical or psychological dependence. However, since it is difficult to predict from experiments the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of buspirone misuse or abuse (eg, development of tolerance, incrementation of dose, drug-seeking behavior).

Overdosage: ***Signs and Symptoms***—At doses approaching 375 mg/day the following symptoms were observed nausea, vomiting, dizziness, drowsiness, miosis, and gastric distress No deaths have been reported in humans either with deliberate or accidental overdosage

Recommended Overdose Treatment—General symptomatic and supportive measures should be used along with immediate gastric lavage No specific antidote is known and dialyzability of buspirone has not been determined

For complete details, see Prescribing Information or consult your Mead Johnson Pharmaceuticals Representative

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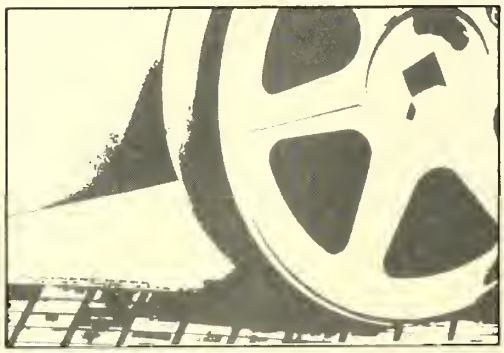

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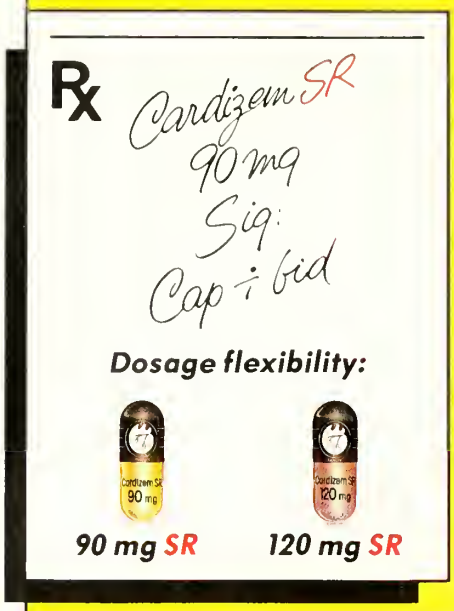

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CONTRAINDICATIONS

CARDIZEM is contraindicated in (1) patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker, (2) patients with second- or third-degree AV block except in the presence of a functioning ventricular pacemaker, (3) patients with hypotension (less than 90 mm Hg systolic), (4) patients who have demonstrated hypersensitivity to the drug, and (5) patients with acute myocardial infarction and pulmonary congestion documented by X-ray on admission.

WARNINGS

1. **Cardiac Conduction**. CARDIZEM prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second- or third-degree AV block (nine of 2,111 patients or 0.43%). Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single dose of 60 mg of diltiazem.
2. **Congestive Heart Failure**. Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). An acute study of oral diltiazem in patients with impaired ventricular function (ejection fraction 24% ± 6%) showed improvement in indices of ventricular function without significant decrease in contractile function (dp/dt). Experience with the use of CARDIZEM (diltiazem hydrochloride) in combination with beta-blockers in patients with impaired ventricular function is limited. Caution should be exercised when using this combination.
3. **Hypotension**. Decreases in blood pressure associated with CARDIZEM therapy may occasionally result in symptomatic hypotension.
4. **Acute Hepatic Injury**. Mild elevations of transaminases with and without concomitant elevation in alkaline phosphatase and bilirubin have been observed in clinical studies. Such elevations were usually transient and frequently resolved even with continued diltiazem treatment. In rare instances, significant elevations in enzymes such as alkaline phosphatase, LDH, SGOT, SGPT, and other phenomena consistent with acute hepatic injury have been noted. These reactions tended to occur early after therapy initiation (1 to 8 weeks) and have been reversible upon discontinuation of drug therapy. The relationship to CARDIZEM is uncertain in some cases, but probable in some. (See PRECAUTIONS.)

PRECAUTIONS

General. CARDIZEM (diltiazem hydrochloride) is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any drug given over prolonged periods, laboratory parameters should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes, however, these changes were reversible with continued dosing.

Dermatological events (see ADVERSE REACTIONS section) may be transient and may disappear despite continued use of CARDIZEM. However, skin eruptions progressing to erythema multiforme and/or exfoliative dermatitis have also been infrequently reported. Should a dermatologic reaction persist, the drug should be discontinued.

Drug Interaction. Due to the potential for additive effects, caution and careful titration are warranted in patients receiving CARDIZEM concomitantly with any agents known to affect cardiac contractility and/or conduction. (See WARNINGS.) Pharmacologic studies indicate that there may be additive effects in prolonging AV conduction when using beta-blockers or digitalis concomitantly with CARDIZEM. (See WARNINGS.)

As with all drugs, care should be exercised when treating patients with multiple medications. CARDIZEM undergoes biotransformation by cytochrome P-450 mixed function oxidase. Coadministration of CARDIZEM with other agents which follow the same route of biotransformation may result in the competitive inhibition of metabolism. Dosages of similarly metabolized drugs, particularly those of low therapeutic ratio or in patients with renal and/or hepatic impairment, may require adjustment when starting or stopping concomitantly administered CARDIZEM to maintain optimum therapeutic blood levels.

Beta-blockers: Controlled and uncontrolled domestic studies suggest that concomitant use of CARDIZEM and beta-blockers or digitalis is usually well tolerated, but available data are not sufficient to predict the effects of concomitant treatment in patients with left ventricular dysfunction or cardiac conduction abnormalities.

Administration of CARDIZEM (diltiazem hydrochloride) concomitantly with propranolol in five normal volunteers resulted in increased propranolol levels in all subjects and bioavailability of propranolol was increased approximately 50%. If combination therapy is initiated or withdrawn in conjunction with propranolol, an adjustment in the propranolol dose may be warranted. (See WARNINGS.)

Cimetidine. A study in six healthy volunteers has shown a significant increase in peak diltiazem plasma levels (58%) and area-under-the-curve (53%) after a 1-week course of cimetidine at 1,200 mg per day and diltiazem 60 mg per day. Ranitidine produced smaller, nonsignificant increases. The effect may be mediated by cimetidine's known inhibition of hepatic cytochrome P-450, the enzyme system probably responsible for the first-pass metabolism of diltiazem. Patients currently receiving diltiazem therapy should be carefully monitored for a change in pharmacological effect when initiating and discontinuing therapy with cimetidine. An adjustment in the diltiazem dose may be warranted.

Digitalis: Administration of CARDIZEM with digoxin in 24 healthy male subjects increased plasma digoxin concentrations approximately 20%. Another investigator found no increase in digoxin levels in 12 patients with coronary artery disease. Since there have been conflicting results regarding the effect of digoxin levels, it is recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing CARDIZEM therapy to avoid possible over- or underdigitalization. (See WARNINGS.)

Anesthetics: The depression of cardiac contractility, conductivity, and automaticity as well as the vascular dilation associated with anesthetics may be potentiated by calcium channel blockers. When used concomitantly, anesthetics and calcium blockers should be titrated carefully.

Carcinogenesis, Mutagenesis, Impairment of Fertility. A 24-month study in rats and a 21-month study in mice showed no evidence of carcinogenicity. There was also no mutagenic response in in vitro bacterial tests. No intrinsic effect on fertility was observed in rats.

Pregnancy. Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/postnatal studies, there was some reduction in early individual pup weights and survival rates. There was an increased incidence of stillbirths at doses of 20 times the human dose or greater.

There are no well-controlled studies in pregnant women, therefore, use CARDIZEM in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. Diltiazem is excreted in human milk. One report suggests that concentrations in breast milk may approximate serum levels. If use of CARDIZEM is deemed essential, an alternative method of infant feeding should be instituted.

Pediatric Use. Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Serious adverse reactions have been rare in studies carried out to date, but it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded from these studies.

The adverse events described below represent events observed in clinical studies of hypertensive patients receiving either CARDIZEM Tablets or CARDIZEM SR Capsules as well as experiences observed in studies of angina and during marketing. The most common events in hypertension studies are shown in a table with rates in placebo patients shown for comparison. Less common events are listed by body system, these include any adverse reactions seen in angina studies that were not observed in hypertension studies. In all hypertensive patients studied (over 900), the most common adverse events were edema (9%), headache (8%), dizziness (6%), asthenia (5%), sinus bradycardia (3%), flushing (3%), and 1° AV block (3%). Only edema and perhaps bradycardia and dizziness were dose related. The most common events observed in clinical studies (over 2,100 patients) of angina patients and hypertensive patients receiving CARDIZEM Tablets or CARDIZEM SR Capsules were (ie, greater than 1%) edema (5.4%), headache (4.5%), dizziness (3.4%), asthenia (2.8%), first-degree AV block (1.8%), flushing (1.7%), nausea (1.6%), bradycardia (1.5%), and rash (1.5%).

DOUBLE BLIND PLACEBO CONTROLLED HYPERTENSION TRIALS

Adverse	Diltiazem N = 315 # pts (%)	Placebo N = 211 # pts (%)
headache	38 (12%)	17 (8%)
AV block first degree	24 (7.6%)	4 (1.9%)
dizziness	22 (7%)	6 (2.8%)
edema	19 (6%)	2 (0.9%)
bradycardia	19 (6%)	3 (1.4%)
ECG abnormality	13 (4.1%)	3 (1.4%)
asthenia	10 (3.2%)	1 (0.5%)
constipation	5 (1.6%)	2 (0.9%)
dyspepsia	4 (1.3%)	1 (0.5%)
nausea	4 (1.3%)	2 (0.9%)
palpitations	4 (1.3%)	2 (0.9%)
polyuria	4 (1.3%)	2 (0.9%)
somnolence	4 (1.3%)	—
alk phos increase	3 (1%)	1 (0.5%)
hypotension	3 (1%)	1 (0.5%)
insomnia	3 (1%)	1 (0.5%)
rash	3 (1%)	1 (0.5%)
AV block second degree	2 (0.6%)	—

In addition, the following events were reported infrequently (less than 1%) with CARDIZEM SR Capsules or CARDIZEM Tablets or have been observed in angina or hypertension trials:

Cardiovascular: Angina, arrhythmia, second- or third-degree AV block (see conduction warning), bundle branch block, congestive heart failure, syncope, tachycardia, ventricular extrasystoles.

Nervous System: Abnormal dreams, amnesia, depression, gait abnormality, hallucinations, nervousness, paresthesia, personality change, tremor.

Gastrointestinal: Anorexia, diarrhea, dry mouth, dysgeusia, mild elevations of SGOT, SGPT, and LDH (see Hepatic Warnings), thirst, vomiting, weight increase.

Dermatological: Petechiae, photosensitivity, pruritus, urticaria.

Other: Amblyopia, CPK increase, dyspnea, epistaxis, eye irritation, hyperglycemia, hyperuricemia, impotence, muscle cramps, nasal congestion, nocturia, osteoarticular pain, sexual difficulties, tinnitus.

The following postmarketing events have been reported infrequently in patients receiving CARDIZEM: alopecia, erythema multiforme, extrapyramidal symptoms, gingival hyperplasia, hemolytic anemia, increased bleeding time, leukopenia, purpura, retinopathy, and thrombocytopenia. There have been observed cases of generalized rash, characterized as leukocytoclastic vasculitis. In addition, events such as myocardial infarction have been observed which are not readily distinguishable from the natural history of the disease in these patients. A definitive cause and effect relationship between these events and CARDIZEM therapy cannot yet be established. Exfoliative dermatitis (proven by rechallenge) has also been reported.

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In Memoriam

(Continued from Page 109)

MARTIN, FRANK H., Oakland. Died Mar 2, 1991, aged 76. Graduate of University of California, College of Medicine, Irvine, 1962. Dr Martin was a member of the Alameda-Contra Costa Medical Association.

❧

MATYCHOWIAK, FRANCIS A., Bakersfield. Died May 25, 1991, aged 65. Graduate of University of Illinois College of Medicine, Chicago, 1950. Licensed in California in 1954. Dr Matychowiak was a member of the Kern County Medical Society.

❧

MAXSON, EUGENE S., Julian. Died Apr 23, 1991, aged 66. Graduate of Loma Linda University School of Medicine, 1949. Licensed in California in 1949. Dr Maxson was a member of the Imperial County Medical Society.

❧

MILLER, EARL M., Stockton. Died Mar 27, 1991, aged 49. Graduate of University of Oregon, Portland, 1967. Licensed in California in 1970. Dr Miller was a member of the San Joaquin County Medical Society.

❧

MILTON, JAMES T., San Diego. Died Mar 12, 1991, aged 89. Graduate of Northwestern University Medical School, Chicago, Illinois, 1931. Dr Milton was a member of the San Diego County Medical Society.

❧

MOMARY, HASSAN M., Madera. Died Mar 29, 1991, aged 66. Graduate of University of California School of Medicine, 1962. Dr Momary was a member of the Fresno-Madera Medical Society.

❧

MOOTOO, SIEGFRIED A., Yucca Valley. Died Apr 10, 1991, aged 62. Graduate of Baylor University College of Medicine, Houston, Texas, 1958. Licensed in California in 1962. Dr Mootoo was a member of the San Bernardino County Medical Society.

❧

MOSSO, JAMES A. Died Mar 23, 1991, aged 48. Graduate of Johns Hopkins University School of Medicine, Baltimore, Maryland, 1967. Licensed in California in 1969. Dr Mosso was a member of the Los Angeles County Medical Association.

❧

NEMETH, LASLO JENO, Sacramento. Died Apr 24, 1991, aged 40. Graduate of Loyola-Stritch School of Medicine, Maywood, Illinois, 1976. Licensed in California in 1977. Dr Nemeth was a member of the Sacramento-El Dorado Medical Society.

RIXFORD, HENRY C., Lodi. Died May 13, 1991, aged 88. Graduate of Stanford University, Stanford, California, 1930. Licensed in California in 1930. Dr Rixford was a member of the San Joaquin County Medical Society.

❧

ROBERTSON, HELEN R., Newport Beach. Died Mar 12, 1991, aged 98. Graduate of New York Medical College, 1916. Dr Robertson was a member of the Orange County Medical Association.

❧

RYDELL, JOHN R., Santa Barbara. Died May 13, 1991, aged 80. Graduate of Harvard Medical School, Boston, Massachusetts, 1943. Licensed in California in 1951. Dr Rydell was a member of the Santa Barbara County Medical Society.

❧

SOKHOS, DIMITRI, Santa Rosa. Died Apr 21, 1991, aged 69. Graduate of National University of Athens, Greece, 1948. Dr Sokhos was a member of the Sonoma County Medical Association.

❧

STRANGE, GERALD, San Francisco. Died Mar 5, 1991, aged 60. Graduate of Howard University College of Medicine, Washington, DC, 1960. Licensed in California in 1960. Dr Strange was a member of the San Francisco Medical Society.

❧

TABOADA, JOSE, San Francisco. Died May 6, 1991, aged 38. Graduate of New York University, 1980. Dr Taboada was a member of the San Francisco Medical Society.

❧

TERRY, HOWARD R., Santa Cruz. Died Mar 29, 1991, aged 67. Graduate of State University of New York, 1947. Licensed in California in 1966. Dr Terry was a member of the Santa Cruz County Medical Society.

❧

WADE, ROBERT M., Campbell. Died Apr 30, 1991, aged 73. Graduate of Northwestern University Medical School, Chicago, Illinois, 1943. Dr Wade was a member of the Santa Clara County Medical Association.

❧

WALTER, NORMAN T., Hayward. Died Mar 28, 1991, aged 61. Graduate of Northwestern University Medical School, Chicago, Illinois, 1956. Dr Walter was a member of the Alameda-Contra Costa Medical Association.

WOOD, PAUL E., Huntington Beach. Died Apr 1991, aged 50. Graduate of George Washington University, Washington, DC, 1967. Dr Wood was a member of the Orange County Medical Association.

❧

WOODRUFF, NATHAN H., JR, Stockton. Died Apr 25, 1991, aged 49. Dr Woodruff was a member of Howard University College of Medicine, Washington, DC, 1972. Dr Woodruff was a member of the San Joaquin County Medical Society.

❧

ZEIGLER, PAUL, Petaluma. Died Mar 1991, aged 83. Graduate of University of Oklahoma, Oklahoma City, 1934. Dr Zeigler was a member of the Sonoma County Medical Association.

Denver Medical Society

HANNUM, JOHN N. Died Apr 19, 1991, aged 69. Graduate of Western Reserve University, Cleveland, Ohio, 1955. Licensed in Colorado in 1955.

❧

MEISTER, EDWARD J. Died Apr 28, 1991, aged 94. Graduate of University of Iowa College of Medicine, Iowa City, 1933. Licensed in Colorado in 1938.

❧

BOB EDWARDS, former Managing Editor of CALIFORNIA MEDICINE, later, THE WESTERN JOURNAL OF MEDICINE, died July 12, 1991, at his home in Calistoga, California. Bob joined the journal in 1946 and served as Assistant to the Editor and Managing Editor until his retirement in 1974.

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ANESTHESIOLOGY

September 7-8—**Case Conference in Anesthesia.** California Society of Anesthesiologists at Horizon Hotel, Lake Tahoe, Nevada. Sat-Sun. 9 hrs. $150. Contact: California Society of Anesthesiologists, 1065 E Hillsdale Blvd, Ste 410, Foster City. (800) 345-3691.

September 14—**Current Concepts in Pediatric Anesthesia.** Children's Hospital, Oakland. Sun. 14 hrs. 7 hrs. $150. Contact: Children's Hospital, 747-52nd St, Oakland 94609. (415) 428-3021.

November 3-9—**Hawaiian Seminar on Clinical Anesthesia.** California Society of Anesthesiologists at Hyatt Regency Hotel, Poipu Beach, Kauai, Hawaii. 1 week. 20 hrs. $415. Contact: CSA, 1065 E Hillsdale Blvd, Ste 410, Foster City 94404. (800) 345-3691.

KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690. (415) 541-0900.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Herbert M. Thomas, MD, MPH, Director of CME, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th St, Los Angeles 90059. (213) 603-3183.

LLU: Loma Linda University
Contact: James J. Couperus, MD, Associate Dean for Educational Affairs, Loma Linda University School of Medicine, Loma Linda 92350.

PMC: Pacific Medical Center
Contact: Continuing Education, Pacific Medical Center, PO Box 7999, San Francisco 94120. (415) 563-4321, ext 2761.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Medical School Office Building, Suite X-365, Stanford 94305-6114 (415) 723-5594

UCD University of California, Davis
Contact: Ruth Feryok, Director, Office of Continuing Medical Education, University of California, Davis, School of Medicine, 2701 Stockton Blvd, Sacramento 95817. (916) 734-5390.

UCI University of California, Irvine
Contact: Melvin I. Marks, MD, Director, Memorial/UCI Center for Health Education, Long Beach Memorial Medical Center, 2801 Atlantic Ave, PO Box 1428, Long Beach, California 90801-1428. (213) 595-3811.

UCLA University of California, Los Angeles Extension
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, PO Box 24902, UCLA, Los Angeles 90024 (213) 825-8423.

UCSD: University of California, San Diego
Contact: Office of Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (619) 534-3940.

UCSF: University of California, San Francisco
Contact: Janet Johnson, Administrative Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143 (415) 476-4251

USC University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 1975 Zonal Ave, KAM314, Los Angeles 90033 (213) 224-7051

November 8-10—**Anesthesiology Update: 1991.** UCD at Monterey Plaza Hotel, Monterey. Fri-Sun. 14 hrs. $370. Contact: UCD.

January 19-21—**Second America-Japan Anesthesia Congress.** International Anesthesia Research Society at Sheraton Waikiki Hotel, Honolulu, Hawaii. Sun-Tue. 14 hrs. $250. Contact: Vicky Larsen, University of Utah School of Medicine, 50 North Medical Drive, Salt Lake City, UT 84132. (801) 581-6115.

January 19-24—**Hawaiian Seminar on Clinical Anesthesia.** California Society of Anesthesiologists at Westin Maui Hotel, Kaanapali Beach, Maui, Hawaii. Sun-Fri. 20 hrs. Contact: California Society of Anesthesiologists, 1065 E Hillsdale Blvd, #410, Foster City 94404. (800) 345-3691.

CARDIOLOGY

August 16-18—**Cardiac Diagnostic Methods and Risk Management.** Medical Education Resources at Disneyland Hotel, Anaheim. Fri-Sun. Contact: Medical Education Resources, 1500 W Canal Ct, Ste 500, Littleton, CO 80120. (800) 421-3756.

October 10-12—**Cardiology Update: 1991.** American College of Cardiology at Quail Lodge, Carmel. Thurs-Sat. 12.5 hrs. $440. Contact: ACC, Extramural Programs, Dept 5080, Washington, DC 20061-5080. (800) 253-4636.

October 18-19—**Coronary Heart Disease Update.** Medical Education Resources at Parc Fifty Hotel, San Francisco. Fri-Sat. Contact: Karen DeBont, MER, 1500 W Canal Ct, Ste 500, Littleton, CO 80120-4528. (800) 421-3756.

October 18-19—**Cardiology for the Clinician.** Memorial/UCI Center for Health Education. Fri-Sat. Contact: UCI.

November 8-9—**Coronary Interventions: 1991.** Scripps Clinic and Research Foundation at La Jolla Marriott Hotel. Fri-Sat. 14 hrs. $550. Contact: Susan Buntjer, 400S, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

CRITICAL CARE

October 17-19—**Traumatic Brain Injury.** UCD at Radisson Hotel, Sacramento. Thurs-Sat. 26 hrs. Contact: UCD.

October 17-19—**10th Annual Recent Advances in Pulmonary and Critical Care Medicine.** UCSF at Sheraton Palace Hotel, San Francisco. Thurs-Sat. 15 hrs. $395. Contact: UCSF.

DERMATOLOGY

August 16-20—**Fifth Annual Hot Spots in Dermatology: Masters Under the Mango Trees.** The Hawaii Dermatology Society and the Kauai Foundation at the Kaluakoi Hotel, Kepuhi Beach, Molokai, Hawaii. Fri-Tues. Contact: David Elpern, MD, Box 457, Kalaheo, HI 96741. (808) 245-1505.

August 26-28—**Dermatology for the Nondermatologist.** Continuing Medical Education Associates at Hotel del Coronado, San Diego. Mon-Wed. Contact: Jacqueline Shiller, Box 84296, San Diego 92138. (619) 223-2997.

November 8-10—**Pediatric Dermatology and Wound Management: Above and Below the Surface.** Children's Hospital Oakland at Monterey Conference Center, Monterey. Fri-Sun. 12 hrs. $300. Contact: Children's Hospital, 747-52nd St, Oakland 94609. (415) 428-3021.

January 17-19—**Practical Dermatology and Dermatologic Office Procedures for the Primary Care Physician.** UCSD at Hyatt Regency, La Jolla. Fri-Sun. 20 hrs. Contact: Jacqueline Shiller, Box 84296, San Diego 92138. (619) 223-2997.

January 31-February 2—**Cutaneous Malignancies: 1992 Skin Cancer Update.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Fri-Sun. 18 hrs. Contact: Susan Buntjer, Scripps Clinic and Research Foundation, 10666 N Torrey Pines Road, La Jolla 92037. (619) 554-8556.

EMERGENCY MEDICINE

August 19-23—**Symposium II: Trauma and Surgery.** UCSD at La Jolla Marriott, La Jolla. Mon-Fri. 32 hrs. $485. Contact: UCSD.

August 23-26—**Advances in Emergency Medicine.** Kaiser Permanente at Grand Hyatt Wailea Resort and Spa, Maui, Hawaii. Fri-Mon. Contact: Pat Salher, MD, Kaiser Permanente Hospital, 2200 O'Farrell, San Francisco 94115-3395.

(Continued on Page 122)

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(Continued from Page 112)

169 **Medical Management of Spinal Cord Injury**
VANCE O. GARDNER, MD, and VINCE CAIOZZO, PhD

170 **Ilizarov Method**
KEVIN W. LOUIE, MD

170 **Update on the Diagnosis and Treatment of Scaphoid Fractures**
ROY A. MEALS, MD

171 **Open Reduction of Pelvic Fractures**
ROBERT BAIRD, MD

172 **Bearing Surfaces in Total Joint Replacement**
RICHARD B. WELCH, MD, and GARY LEVENGOOD, MD

172 **Arthroscopic-assisted Reconstruction of the Anterior Cruciate Ligament**
RICHARD A. MARDER, MD

172 **Percutaneous Discectomy**
JAMES M. MORRIS, MD

173 **Objective Measurements for Rehabilitation After Back Injury**
VERT MOONEY, MD

ALERTS, NOTICES, AND CASE REPORTS

174 **Superior Mesenteric Artery Thrombosis Associated With Antiphospholipid Syndrome**
MAURICE E. HAMILTON, MD

From the Division of Rheumatology, Allergy, and Clinical Immunology, University of California, Davis, Medical Center, Sacramento.

176 **Metastasis-induced Acute Pancreatitis**
SHAUN S. J. HUNG, MD, and BACH ARDALAN, MD

From the Department of Oncology, University of Miami School of Medicine, Florida. Dr Hung is now with the Department of Medicine, Kaiser Permanente Medical Center, Santa Clara, California.

178 **Spontaneous Intracranial Hypotension—An Uncommon and Underrecognized Cause of Headache**
MICHAEL B. JACOBS, MD, and PHILIP H. WASSERSTEIN, MD

From the Departments of Medicine and Neurology, Stanford University Medical Center, Stanford, California.

RADIOLOGIC CASE

181 **Lung Mass and Hemoptysis in a Patient With Tuberculosis**
KRISHNAN PADMANABHAN, MD; SANTI R. DHAR, MD; and KIAT YEO, MD

From the Department of Pulmonary Medicine, Coney Island Hospital, Brooklyn, New York, and the Department of Medicine, State University of New York, Health Science Center at Brooklyn, College of Medicine.

COMMENTARY

183 **The Perils of Providing Medical Opinion—A State Medical Association's Experience**
HIBBARD E. WILLIAMS, MD, and LINDA L. RAMSEY

From the Scientific Board and Division of Scientific and Educational Activities, California Medical Association, San Francisco, and the University of California, Davis, School of Medicine.

(Continued on Page 124)

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CONTINUING MEDICAL EDUCATION

(Continued from Page 118)

October 28-November 1—**Twentieth Annual Topics in Emergency Medicine.** UCSF at Sheraton Palace Hotel, San Francisco. Mon-Fri. 32 hrs. $510. Contact: UCSF.

ENDOCRINOLOGY AND METABOLISM

October 18-20—**Obesity Update: Assessment & Treatment.** UCD at Hyatt Regency, Sacramento. Fri-Sun. Contact: UCD.

October 20-23—**Joint Annual Research Conference on Obesity & Food Intake.** North American Association of the Study of Obesity & Society for Study of Ingestive Behavior at Hyatt Regency, Saramento. Sun-Wed. Contact: UCD.

November 1-2—**Practical Methods in Diabetes.** Memorial/UCI Center for Health Education at Meridien Newport Beach. Fri-Sat. Contact: UCD.

FAMILY PRACTICE/PRIMARY CARE

August 23-25—**Cardiology for the Family Physician and Internist.** Continuing Medical Education Associates at Hotel del Coronado, San Diego. Fri-Sun. Contact: Jacqueline Shiller, Box 84296, San Diego 92138. (619) 223-2997.

August 23-25—**4th Coronado Summer Conference on Primary Care Medicine: A Practical Approach.** Scripps Clinic and Research Foundation at Le Meridien Hotel, San Diego. Fri-Sun. 16 hrs. $275. Contact: Laurie Jones, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-9592.

October 2-4—**Sixth Annual Primary Care Medicine: Principles and Practice.** UCSF at Sheraton Palace Hotel, San Francisco. Wed-Fri. 19 hrs. $465. Contact: UCSF.

October 18-20—**Office Orthopedics for the Primary Care Physician.** Sharp Memorial Hospital at San Diego Princess at Vacation Village. Fri-Sun. 20 hrs. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

GASTROENTEROLOGY

September 20-22—**Gastroenterology: Recent Developments in Theory & Practice.** UCSF at Sheraton Palace Hotel, San Francisco. Fri-Sun. 18 hrs. $420. Contact: UCSF.

INTERNAL MEDICINE

August 18-23—**New Advances in Internal Medicine.** UCD at Hyatt Regency, Monterey. Sun-Fri. 25 hrs. $475. Contact: UCD.

August 26-30—**Internal Medicine Board Review.** Stanford University Medical Center. Mon-Fri. Contact: STAN.

September 6-7—**Cancer Detection & Management.** UCD at Cancer Center Auditorium. Fri-Sat. 12 hrs. Contact: UCD.

September 28—**Pain: Diagnosis, Treatment and Management.** Scripps Clinic and Research Foundation, La Jolla. Sat. 19 hrs. $75. Contact: Laurel Steigerwald, 10666 N Torrey Pines Road, La Jolla 92037. (619) 554-8556.

October 14-20—**Seventeenth Annual Lymphoma Course.** Scripps Clinic and Research Foundation, La Jolla. Mon-Fri. 25 hrs. $550. Contact: Laurel Steigerwald, 10666 N Torrey Pines Road, La Jolla 92037. (619) 554-8556.

November 2—**Cardiac Risk Reduction Conference.** UCD at Radisson Hotel, Sacramento. Sat. Contact: UCD.

November 7-9—**San Francisco Otology Update: 1991.** UCSF. Thurs-Sat. 22 hrs. Contact: UCSF.

November 15-16—**Pain Management.** UCD at Sterling Hotel, Napa. Fri-Sat. Contact: UCD.

November 21-23—**3rd Annual Symposium on Diagnosis and Treatment of Bone and Soft Tissue Tumors.** UCD at Hyatt Regency, Sacramento. Thurs-Sat. 16 hrs. $450. Contact: UCD.

December 5—**Common Musculoskeletal Problems—Knee.** VA Medical Center Sepulveda. Thurs. 5.5 hrs. Contact: Arun Mehta, MD, VA Med Ctr, (818) 895-9344.

December 6-7—**Clinical Applications of New Advances in Internal Medicine.** UCD at Cancer Center Auditorium. Fri-Sat. Contact: UCD.

December 11-15—**American Back Society Fall Symposium on Back Pain.** St. Francis Memorial Hospital Spine Center at Marriott Hotel, San Francisco. Contact: Aubrey A. Swartz, 2647 E 14th St, #401, Oakland 94601. (415) 536-9929.

January 1-February 1—**15th Annual: Neurology for Non-Neurologists.** UCSD at Omni San Diego Hotel, San Diego. Thurs-Sat. 21 hrs. $425. Contact: UCSD.

January 25-February 1—**15th Annual: Infectious Diseases in Clinical Practice.** UCSF at Beaver Run Resort and Conference Center, Breckenridge, Colorado. Sat-Sat. 24 hrs. Contact: UCSF.

OB/GYN

August 16-18—**Office Gynecology for the Primary Care Physician.** San Diego State University at the Hyatt Islandia, San Diego. Fri-Sun. Contact: Jacqueline Shiller, Box 84296, San Diego 92138. (619) 223-2997.

September 26-29—**Advanced Fetal Heart Rate Monitoring.** Memorial/UCI Center for Health Education. Thurs-Sun. Contact: UCI.

October 4-6—**3rd Annual Advanced Obstetrical & Transvaginal Ultrasound.** Memorial/UCI Center for Health Education at Doubletree Hotel/UCI Medical Center, Orange. Fri-Sun. Contact: UCI.

November 8-10—**Current Issues in Perinatal Medicine.** Memorial/UCI at Marriott's Rancho Las Palmas Resort, Palm Springs. Fri-Sun. Contact: UCI.

November 18-23—**14th Annual Review Course in Clinical Ob/Gyn and Gynecological Histopathology.** Memorial/UCI Center for Health Education at Westin South Coast Plaza, Costa Mesa. Mon-Sat. Contact: UCI.

October 23-26—**Trends in OB-GYN Management.** Sharp Memorial Hospital at Hotel del Coronado, San Diego. Wed-Sat. 16 hrs. Contact: Debra L. Gist, 7901 Frost St, San Diego 92123-2788. (619) 541-4530.

OCCUPATIONAL/ENVIRONMENTAL

September 28—**Indoor Air and Radon: Reducing Health Risks Forum.** CMA, AMA, and US EPA at LAX Marriott, Los Angeles. Sat. 4 hrs. Contact: Vickie Grosso. (312) 464-4574.

October 10-13—**35th Annual Western Occupational Health Conference: Changing Themes in Occupational Medicine.** Western Occupational Medical Association at Doubletree Hotel, Monterey. Thurs-Sun. Contact: Kate Larsen, (415) 764-4803.

October 21-25—**Sports Medicine Update.** Memorial/UCI Center for Health Education in Hawaii. Mon-Fri. Contact: UCI.

October 21-November 1—**Occupational and Environmental Medicine: Session II.** UCSF at Miyako Hotel, San Francisco. Mon-Fri. 80 hrs. $1200. Contact: UCSF.

October 28-November 1—**Advances in Occupational and Environmental Medicine.** UCSF at Miyako Hotel, San Francisco. Mon-Fri. 40 hrs. $600. Contact: UCSF.

January 27-February 7—**Occupational and Environmental Medicine Series: Session I.** UCSF at Miyako Hotel, San Francisco. Mon-Fri. 80 hrs. $1200. Contact: UCSF.

OPHTHALMOLOGY

September 13-15—**Uveitis and Retina Frontiers—Diagnostic, Medical and Surgical Approaches.** UCSF at Carmel Valley Ranch Resort. Fri-Sun. Contact: UCSF.

October 13-17—**Joint Meeting of the American Academy of Ophthalmology and Pan-American Association of Ophthalmology** at Anaheim Convention Center. Sun-Thurs. Contact: AAO, PO Box 7424, San Francisco 94120. (415) 561-8500.

PATHOLOGY

October 12—**Thirty-first Annual Scientific Symposium on Kidney Disease.** National Kidney Foundation of Southern California at La Jolla Marriott, La Jolla. Sat. Contact: Sylvie Tarro, (213) 641-8152.

PEDIATRICS

August 19-21—**Pediatrics Update: 1991.** San Diego State University at the Hyatt Islandia, San Diego. Mon-Wed. Contact: Jacqueline Shiller, Box 84296, San Diego 92138. (619) 223-2997.

September 13-14—**Ambulatory Pediatrics.** UCD at Radisson Hotel, Sacramento. Fri-Sat. 12 hrs. Contact: UCD.

September 23-27—**Pediatrics in Paradise.** Valley Children's Hospital at Hyatt Regency, Kauai, Hawaii. Mon-Fri. 20 hrs. Contact: Valley Children's Hospital, Marketing and Planning, 3151 N Millbrook, Fresno 93703.

October 16-19—**16th Annual Pediatrics for the Practitioner.** Memorial/UCI Center for Health Education at Mauna Kea Beach Hotel, Kamuela, Hawaii. Wed-Sat. Contact: UCI.

(Continued on Page 127)

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(Continued from Page 120)

Medical Education, Training, and Health Care Services in the Republic of Singapore
CHIN HIN CHEW, MD, FACP, FRCP, FRACP
From the Academy of Medicine, Republic of Singapore.

EDITORIALS

189 **Understanding Autocrine Growth Regulation**
ROBERT J. COFFEY, MD, and JOHN A. BARNARD, MD
From the Departments of Medicine and Cell Biology, Division of Gastroenterology, and the Division of Pediatric Gastroenterology, Vanderbilt University School of Medicine, Nashville, Tennessee.

CORRESPONDENCE

191 **Abortion 'Gag' Rule**
HERBERT NOTKIN, MD

191 **Do We Need Warning Labels on Food?**
ALVIN R. LOOSLI, MD
JOSEPH E. SCHERGER, MD
THOMAS BODENHEIMER, MD, MPH, responds

LESSONS FROM THE PRACTICE

193 **Routine Gone Awry**
CARL COPPOLA, MD
From the Department of Otolaryngology, University of Southern California School of Medicine, and the Department of Otolaryngology-Head and Neck Surgery, Los Angeles County-USC Medical Center, Los Angeles.

OTHER FEATURES

109 **In Memoriam**

118 **Continuing Medical Education Activities in California, Hawaii, and Nevada; Colorado; Idaho; New Mexico; Utah; Washington; Wyoming**

130 **Subscription Information**

194 **Poem**

195 **Instructions for Authors**

202 **Classified Advertising**

212 **Western State Medical Associations' Meetings**

★ Official Journal of the Alaska State Medical Association, the Arizona Medical Association, the California Medical Association, the Denver Medical Society, the Idaho Medical Association, the Nevada State Medical Association, the New Mexico Medical Society, the Utah Medical Association, the Washington State Medical Association, and the Wyoming Medical Society.

★ Affiliated Clinical Investigation Societies: the Western Association of Physicians; the Western Society for Clinical Investigation; the Western Section, American Federation for Clinical Research; the Western Society for Pediatric Research; the Western Region, Society for Investigative Dermatology.

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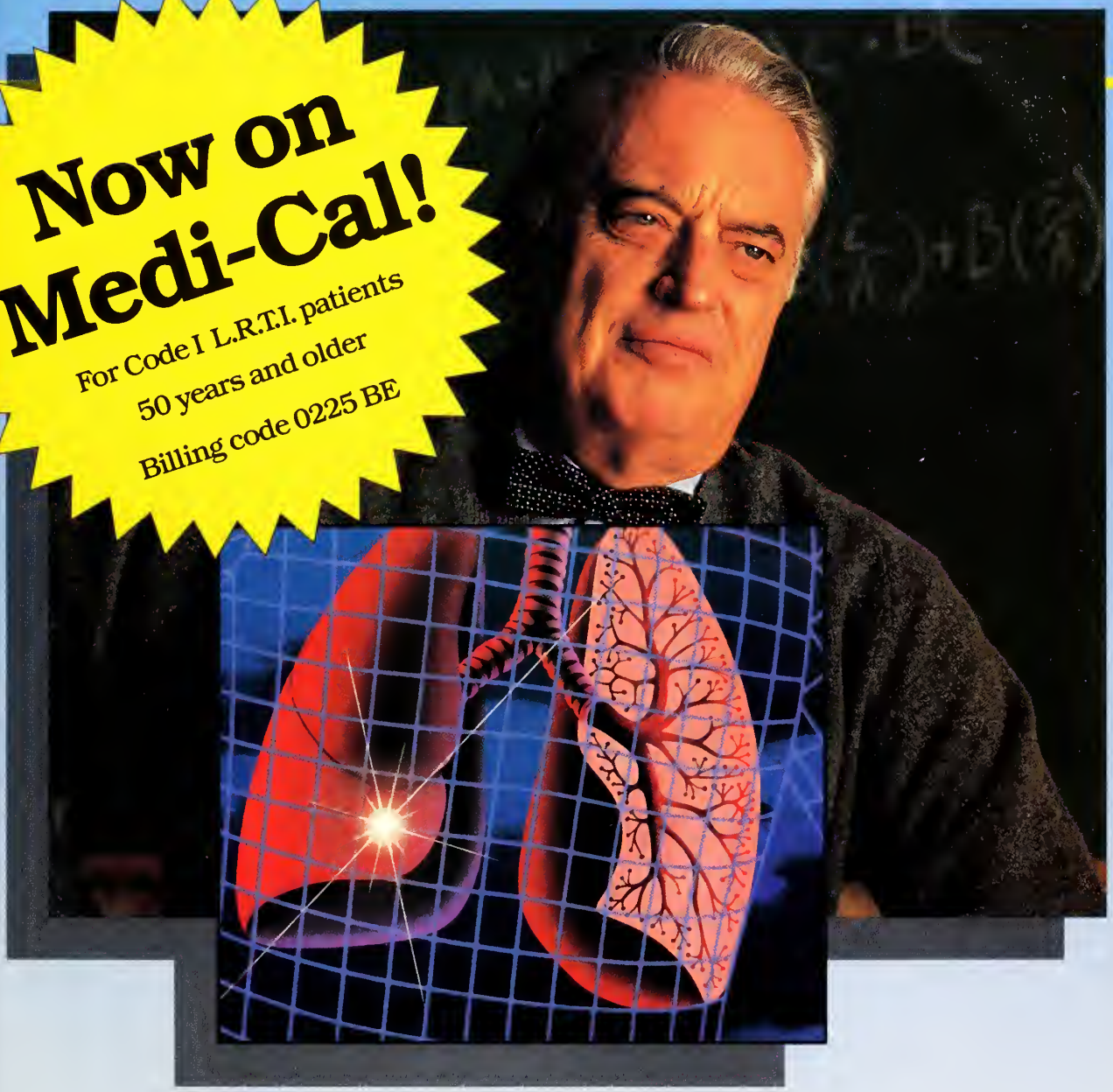

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amoxicillin/clavulanate potassium

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Philadelphia, PA 19101

Brief Summary of Prescribing Information

AUGMENTIN amoxicillin/clavulanate potassium

Indications and Usage. *Augmentin* is indicated in the treatment of infections caused by susceptible strains of the designated organisms in the conditions listed below

Lower Respiratory Infections caused by β-lactamase-producing strains of *Hemophilus influenzae* and *Branhamella catarrhalis*

Otitis Media caused by β-lactamase-producing strains of *Hemophilus influenzae* and *Branhamella catarrhalis*

Sinusitis caused by β-lactamase-producing strains of *Hemophilus influenzae* and *Branhamella catarrhalis*

Skin and Skin Structure Infections caused by β-lactamase-producing strains of *Staphylococcus aureus*, *E. coli*, and *Klebsiella* spp.

Urinary Tract Infections caused by β-lactamase-producing strains of *E. coli*, *Klebsiella* spp. and *Enterobacter* spp.

While *Augmentin* is indicated only for the conditions listed above, infections caused by ampicillin-susceptible organisms are also amenable to *Augmentin* treatment due to its amoxicillin content. Therefore, mixed infections caused by ampicillin susceptible organisms and β-lactamase-producing organisms susceptible to *Augmentin* should not require the addition of another antibiotic.

Bacteriological studies, to determine the causative organisms and their susceptibility to *Augmentin*, should be performed together with any indicated surgical procedures.

Therapy may be instituted prior to obtaining the results from bacteriological and susceptibility studies to determine the causative organisms and their susceptibility to *Augmentin* when there is reason to believe the infection may involve any of the β-lactamase-producing organisms listed above. Once the results are known, therapy should be adjusted, if appropriate.

Contraindications: A history of allergic reactions to any penicillin is a contraindication.

WARNINGS: SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTOID) REACTIONS HAVE BEEN REPORTED IN PATIENTS ON PENICILLIN THERAPY. ALTHOUGH ANAPHYLAXIS IS MORE FREQUENT FOLLOWING PARENTERAL THERAPY, IT HAS OCCURRED IN PATIENTS ON ORAL PENICILLINS. THESE REACTIONS ARE MORE LIKELY TO OCCUR IN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY AND/OR A HISTORY OF SENSITIVITY TO MULTIPLE ALLERGENS. THERE HAVE BEEN REPORTS OF INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE REACTIONS WHEN TREATED WITH CEPHALOSPORINS. BEFORE INITIATING THERAPY WITH ANY PENICILLIN, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS, OR OTHER ALLERGENS. IF AN ALLERGIC REACTION OCCURS, *AUGMENTIN* SHOULD BE DISCONTINUED AND THE APPROPRIATE THERAPY INSTITUTED. **SERIOUS ANAPHYLACTOID REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE, OXYGEN, INTRAVENOUS STEROIDS, AND AIRWAY MANAGEMENT, INCLUDING INTUBATION. SHOULD ALSO BE ADMINISTERED AS INDICATED.**

Precautions General: While *Augmentin* possesses the characteristic low toxicity of the penicillin group of antibiotics, periodic assessment of organ system functions, including renal, hepatic and hematopoietic function, is advisable during prolonged therapy.

A high percentage of patients with mononucleosis who receive ampicillin develop a skin rash. Thus, ampicillin class antibiotics should not be administered to patients with mononucleosis.

The possibility of superinfections with mycotic or bacterial pathogens should be kept in mind during therapy. If superinfections occur (usually involving *Pseudomonas* or *Candida*) the drug should be discontinued and/or appropriate therapy instituted.

Drug Interactions: Probenecid decreases the renal tubular secretion of amoxicillin. Concurrent use with *Augmentin* may result in increased and prolonged blood levels of amoxicillin.

The concurrent administration of allopurinol and ampicillin increases substantially the incidence of rashes in patients receiving both drugs as compared to patients receiving ampicillin alone. It is not known whether this potentiation of ampicillin rashes is due to allopurinol or the hyperuricemia present in these patients. There are no data with *Augmentin* and allopurinol administered concurrently.

Augmentin should not be co-administered with Antabuse® (disulfiram).

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have not been performed to evaluate carcinogenic or mutagenic potential.

Pregnancy (Category B): Reproduction studies have been performed in mice and rats at doses up to ten (10) times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to *Augmentin*. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery: Oral ampicillin class antibiotics are generally poorly absorbed during labor. Studies in guinea pigs have shown that intravenous administration of ampicillin decreased the uterine tone, frequency of contractions, height of contractions and duration of contractions. However, it is not known whether the use of *Augmentin* in humans during labor or delivery has immediate or delayed adverse effects on the fetus, prolongs the duration of labor or increases the likelihood that forceps delivery or other obstetrical intervention or resuscitation of the newborn will be necessary.

Nursing Mothers: Ampicillin class antibiotics are excreted in the milk; therefore, caution should be exercised when *Augmentin* is administered to a nursing woman.

Adverse Reactions: *Augmentin* is generally well tolerated. The majority of side effects observed in clinical trials were of a mild and transient nature and less than 3% of patients discontinued therapy because of drug-related side effects. The most frequently reported adverse effects were diarrhea/loose stools (9%), nausea (3%), skin rashes and urticaria (3%), vomiting (1%) and vaginitis (1%).

The overall incidence of side effects, and in particular diarrhea, increased with the higher recommended dose. Other less frequently reported reactions include abdominal discomfort, flatulence and headache.

The following adverse reactions have been reported for ampicillin class antibiotics:

Gastrointestinal: Diarrhea, nausea, vomiting, indigestion, gastritis, stomatitis, glossitis, black "hairy" tongue, enterocolitis and pseudomembranous colitis.

Hypersensitivity reactions: Skin rashes, urticaria, angioedema, serum sickness-like reactions (urticaria or skin rash accompanied by arthritis/arthralgia, myalgia, and frequently fever), erythema multiforme (rarely Stevens-Johnson Syndrome), and an occasional case of exfoliative dermatitis have been reported. These reactions may be controlled with antihistamines and, if necessary, systemic corticosteroids. Whenever such reactions occur, the drug should be discontinued, unless the opinion of the physician dictates otherwise. Serious and occasional fatal hypersensitivity (anaphylactic) reactions can occur with oral penicillin (See Warnings).

Liver: A moderate rise in SGOT, SGPT, AST, and/or ALT has been noted in patients treated with ampicillin class antibiotics including *Augmentin*. The significance of these findings is unknown. As with some other penicillins and some cephalosporins, hepatic dysfunction has been reported rarely, with the predominant effects being cholestatic, hepatocellular, or mixed cholestatic-hepatocellular. Signs/symptoms may appear during or after therapy and they resolve completely over time.

Hemic and Lymphatic Systems: Anemia, thrombocytopenia, thrombocytopenic purpura, eosinophilia, leukopenia and agranulocytosis have been reported during therapy with penicillins. These reactions are usually reversible on discontinuation of therapy and are believed to be hypersensitivity phenomena. A slight thrombocytosis was noted in less than 1% of the patients treated with *Augmentin*.

Central Nervous System: Reversible hyperactivity, agitation, anxiety, insomnia, confusion, behavioral changes, and/or dizziness have been reported rarely.

Dosage Adults: The usual adult dose is one *Augmentin* '250' tablet every eight hours. For more severe infections and infections of the respiratory tract, the dose should be one *Augmentin* '500' tablet every eight hours.

Since both the *Augmentin* '250' and '500' tablets contain the same amount of clavulanic acid (125 mg, as the potassium salt), two *Augmentin* '250' tablets are not equivalent to one *Augmentin* '500' tablet. Therefore, two *Augmentin* '250' tablets should not be substituted for one *Augmentin* '500' tablet for treatment of more severe infections.

Children: The usual dose is 20 mg/kg/day, based on amoxicillin component, in divided doses every eight hours. For otitis media, sinusitis and other more severe infections, the dose should be 40 mg/kg/day, based on the amoxicillin component, in divided doses every eight hours. Also available as *Augmentin* '125' and '250' chewable tablets.

Children weighing 40 kg and more should be dosed according to the adult recommendations.

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(Continued from Page 122)

November 20-23—**Pediatric Infectious Disease Seminar.** University of Toronto at Four Seasons Hotel, Newport Beach. Wed-Sat. Contact: University of Toronto, Medical Science Bldg, Toronto, Ontario M5S 1A8. (416) 978-2718.

January 22-25—**San Diego Conference on Responding to Child Maltreatment.** Children's Hospital at Hyatt Regency Hotel, La Jolla. Wed-Sat. Contact: Children's Hospital, 8001 Frost St, San Diego 92123. (619) 495-4940.

PSYCHIATRY

November 8-10—**37th Annual Group Therapy Symposium.** UCSF at Handlery Union Square Hotel, San Francisco. Fri-Sun. Contact: UCSF.

RADIOLOGY

September 5-8—**Physics of Diagnostic Radiology, Nuclear Medicine and Radiation Biology.** UCD. Thurs-Sun. 25 hrs. $395. Contact: UCD.

September 11-13—**The 7th Annual Sonography Update Conference and Exhibit.** UCSD at Hotel del Coronado, San Diego. Wed-Fri. 18 hrs. $400. Contact: Dawne Ryals, Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

September 14-15—**Sonography Registry Review.** UCSD at Hotel del Coronado, San Diego. Sat-Sun. 16 hrs. $200. Contact: Dawne Ryals, Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

September 23-26—**Applied Ultrasound: Accent on Doppler.** University of Alabama at Birmingham at Ritz-Carlton Resort Hotel, Laguna Niguel. Mon-Thurs. Contact: Dawne Ryals, Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

September 25-28—**Diagnosis of Musculoskeletal Disorders: State of the Art.** International Skeletal Society at Hotel del Coronado, San Diego. Wed-Sat. 28 hrs. $450. Contact: Dawne Ryals, Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

October 2-6—**Current Concepts of Magnetic Resonance Imaging/Physics.** Stanford University Medical Center at Silverado Hotel, Napa Valley. Wed-Mon. 19 hrs. $500. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

October 12-13—**Ultrasound: 1991.** UCD at Red Lion Inn, Sacramento. Sat-Sun. 10 hrs. $215. Contact: UCD.

October 17-20—**1991 Annual Scientific Meeting.** Western Neuroradiological Society at Ritz Carlton Resort, Laguna Niguel. Thurs-Sun. Contact: Dawne Ryals, Ryals & Associates, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

October 20—**Magnetic Resonance Angiography.** UCSF at Hyatt Regency Hotel, San Francisco. Sun. 7 hrs. Contact: UCSF.

October 21-25—**Clinical Magnetic Resonance Imaging.** UCSF at Hyatt Regency Hotel, San Francisco. Mon-Fri. 32 hrs. $595. Contact: UCSF.

October 26-27—**Advanced Imaging of the Musculoskeletal System.** UCSD at Hotel del Coronado, San Diego. Sat-Sun. 9 hrs. $225. Contact: Dawne Ryals, Ryals & Associates, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

October 26-27—**Vascular Ultrasound: State of the Art.** UCSF at Ritz-Carlton Hotel, San Francisco. Sat-Sun. 12 hrs. $285. Contact: UCSF.

October 28-November 1—**Sixteenth Annual Postgraduate Radiology Course.** UCSD at Hotel del Coronado, San Diego. Mon-Fri. 28.25 hrs. $550. Contact: Dawne Ryals, Ryals & Associates, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

November 1-3—**11th Annual Interventional Radiology Course.** UCSD at Hotel del Coronado, San Diego. Fri-Sun. 15 hrs. $375. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

November 4-8—**Diagnostic Radiology Seminars.** UCSF at Hyatt Regency, Maui, Hawaii. Mon-Fri. 24 hrs. $595. Contact: UCSF.

November 15-17—**Advanced Seminars in Diagnostic Imaging.** UCSD at Ritz-Carlton Hotel, Laguna Niguel. Fri-Sun. $400. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

REHABILITATIVE/THERAPEUTIC

October 5—**Antithrombotic Therapy.** UCD at Cancer Center Auditorium. Sat. 6 hrs. Contact: UCD.

November 14-16—**3rd Triennial Symposium on New Directions in Antiviral Chemotherapy.** UCSF at Sheraton Palace Hotel, San Francisco. Thurs-Sat. 19 hrs. $200. Contact: UCSF.

SURGERY

September 12-13—**Advanced Endoscopic Surgery.** UCD. Thurs-Fri. 17 hrs. $3200. Contact: UCD.

October 10-13—**Wound Management Workshop: October.** UCSD at San Diego Hilton Beach and Tennis Resort. Thurs-Sun. 18 hrs. $435. Contact: Edith Bookstein, PO Box 2586, La Jolla 92038. (619) 454-3212.

October 27-30—**Preparing for Surgery: Medical Evaluation of the Preoperative Patient.** American College of Physicians and UCD at La Playa Hotel, Carmel. Sun-Wed. Contact: ACP, Independence Mall West, 6th St at Race, Philadelphia, PA 19106-1572. (800) 523-1546, ext. 2429.

November 2-9—**13th International Seminar on Operative Arthroscopy.** UCLA at Ritz-Carlton, Mauna Lani Resort, Hawaii. 1 week. 37 hrs. $995. Contact: UCLA.

GENERAL/MULTIDISCIPLINARY

December 9-10—**Clinical Care of the AIDS Patient.** UCSF at San Francisco Marriott Hotel. Mon-Tues. 13 hrs. $250. Contact: UCSF.

COLORADO

This listing of continuing medical education programs in Colorado is compiled by the Denver Medical Society. To list CME programs here, please send information at least two months in advance to: Mr Robert L. Kennedy, Denver Medical Society, 1850 Williams Street, Denver, CO 80218; or telephone (303) 377-1850.

Brochures, course information, and registration forms are available from the contact person or organization.

July 22-26—**Renal Disease for the Internist and Nephrologist.** University of Colorado School of Medicine at The Given Institute, Aspen. Mon-Fri. Contact: Joann Bauer, (303) 270-5195 or (800) 882-9513.

July 25-27—**Preparing for Reform—Proposals, Assumptions and Implications for Financing American Health Care—11th Annual Montgomery Dorsey Symposium.** Presbyterian/St. Luke's Community Foundation at Vail. Thurs-Sat. Contact: Mary Pettigrew, (303) 322-3515.

July 29-August 2—**Dynamic Psychotherapy.** University of Colorado School of Medicine at The Given Institute, Aspen. Mon-Fri. Contact: Joann Bauer, (303) 270-5195 or (800) 882-9513.

August 2-4—**Recent Advances in Cancer Therapy.** University of Colorado School of Medicine at The Given Institute, Aspen. Fri-Sun. Contact: Joann Bauer, (303) 270-5195 or (800) 882-9153.

August 4-8—**34th Annual Pediatric Program.** University of Colorado School of Medicine, Children's Hospital, and the Colorado Chapter of the American Academy of Pediatrics at the Given Institute, Aspen. Sun-Thurs. Contact: Bobbi Rubingh, (800) 882-9153 or (303) 270-5196.

August 5-9—**Respiratory Therapy Traineeship Program.** Children's Hospital, Denver. Mon-Fri. Contact: Jeff Griebel, (303) 861-6188.

August 8—**Basic and Advanced Fetal Heart Rate Monitoring.** University of Colorado Health Sciences Center, Denver. Thurs. Contact: Trish Beachy or Nancy Briggs, (303) 270-7117.

August 8-11—**Pulmonary Physiology.** University of Colorado School of Medicine at The Given Institute, Aspen. Thurs-Sun. Contact: Joann Bauer, (303) 270-5195 or (800) 882-9153.

August 15-17—**Musculoskeletal Society Annual Meeting.** In association with University of Colorado School of Medicine at Snowmass. Contact: Joann Bauer, (303) 270-5195 or (800) 882-9153.

August 17-24—**Eleventh Annual Comprehensive Fine Needle Biopsy Course.** University of California, San Francisco, at Aspen's Hotel Jerome. Sat-Sat. Contact: University of California, San Francisco, School of Medicine, Extended Programs in Medical Education, (415) 476-4251.

August 19-23—**Internal Medicine Board Review.** University of Colorado School of Medicine, Denver. Mon-Fri. Contact: Joann Bauer, (303) 270-5195 or (800) 882-9153.

August 20—**Vascular Occlusion of the Retina.** Lutheran Medical Center, Wheat Ridge. Tues. Contact: Cary L. Walker, (303) 425-2009.

August 25-31—**Primary Care Orthopedics.** University of Colorado School of Medicine at The Given Institute, Aspen. Sun-Sat. Contact: Joann Bauer, (303) 270-5195 or (800) 882-9153.

August 27—**The Evaluation of the Hoarse Voice.** Lutheran Medical Center, Wheat Ridge. Tues. Contact: Cary L. Walker, (303) 425-2009.

September 5, 12, 19, 26—**Comprehensive Perinatal Nursing Course.** University of Colorado Health Sciences Center. Thurs. Contact: Trish Beachy or Nancy Briggs, (303) 270-7117.

September 13-14—**Colorado Post-Polio Connection 1991 Education Conference.** Colorado Easter Seal Society for Handicapped Children and Adults, Inc, at Westin Hotel at The Tabor Center, Denver. Fri-Sat. Contact: Alison Kron, (303) 233-1666.

(Continued on Page 131)

96% of patients don't ask about their medicines,[1] but 72% want more information.[2]

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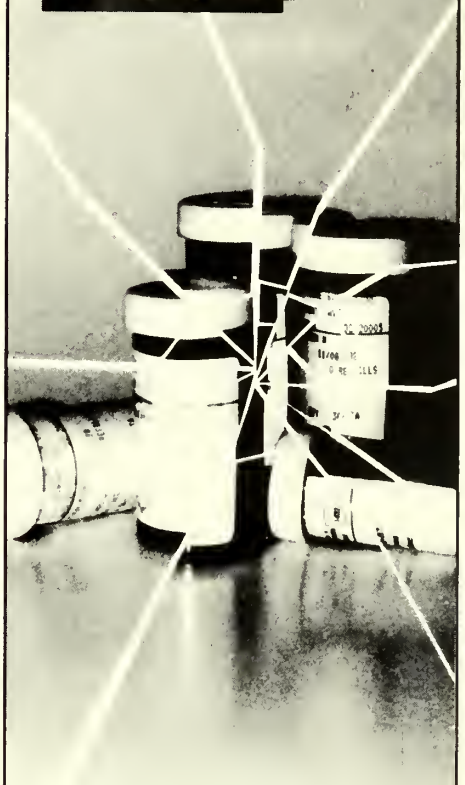

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[1] FDA survey, "Patient Receipt of Rx Drug Information", 1983

[2] A Study of Attitudes, Concerns, and Information Needs for Rx Drugs and Related Illnesses, CBS Television Network Consumer Model Survey, 1983

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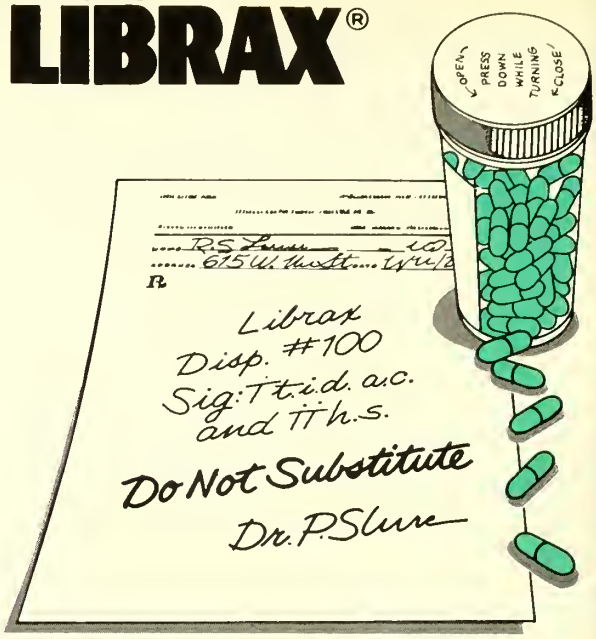

Each capsule contains 5 mg chlordiazepoxide HCl and 2.5 mg clidinium bromide.

Please consult complete prescribing information, a summary of which follows:

Indications: Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:
"Possibly" effective: as adjunctive therapy in the treatment of peptic ulcer and in the treatment of the irritable bowel syndrome (irritable colon, spastic colon, mucous colitis) and acute enterocolitis.
Final classification of the less-than-effective indications requires further investigation.

Contraindications: Glaucoma; prostatic hypertrophy, benign bladder neck obstruction; hypersensitivity to chlordiazepoxide HCl and/or clidinium Br.
Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants, and against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving).
Usage in Pregnancy: **Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy. Advise patients to discuss therapy if they intend to or do become pregnant.**
As with all anticholinergics, inhibition of lactation may occur.
Withdrawal symptoms of the barbiturate type have occurred after discontinuation of benzodiazepines (see Drug Abuse and Dependence).
Precautions: In elderly and debilitated, limit dosage to smallest effective amount to preclude ataxia, oversedation, confusion (no more than 2 capsules/day initially; increase gradually as needed and tolerated). Though generally not recommended, if combination therapy with other psychotropics seems indicated, carefully consider pharmacology of agents, particularly potentiating drugs such as MAO inhibitors, phenothiazines. Observe usual precautions in presence of impaired renal or hepatic function. Paradoxical reactions reported in psychiatric patients. Employ usual precautions in treating anxiety states with evidence of impending depression; suicidal tendencies may be present and protective measures necessary. Variable effects on blood coagulation reported very rarely in patients receiving the drug and oral anticoagulants; causal relationship not established. Inform patients to consult physician before increasing dose or abruptly discontinuing this drug.
Adverse Reactions: No side effects or manifestations not seen with either compound alone reported with Librax. When chlordiazepoxide HCl is used alone, drowsiness, ataxia, confusion may occur, especially in elderly and debilitated; avoidable in most cases by proper dosage adjustment, but also occasionally observed at lower dosage ranges. Syncope reported in a few instances. Also encountered: isolated instances of skin eruptions, edema, minor menstrual irregularities, nausea and constipation, extrapyramidal symptoms, increased and decreased libido—all infrequent, generally controlled with dosage reduction; changes in EEG patterns may appear during and after treatment; blood dyscrasias (including agranulocytosis), jaundice, hepatic dysfunction reported occasionally with chlordiazepoxide HCl, making periodic blood counts and liver function tests advisable during protracted therapy. Adverse effects reported with Librax typical of anticholinergic agents, *i.e.*, dryness of mouth, blurring of vision, urinary hesitancy, constipation. Constipation has occurred most often when Librax therapy is combined with other spasmolytics and/or low residue diets.
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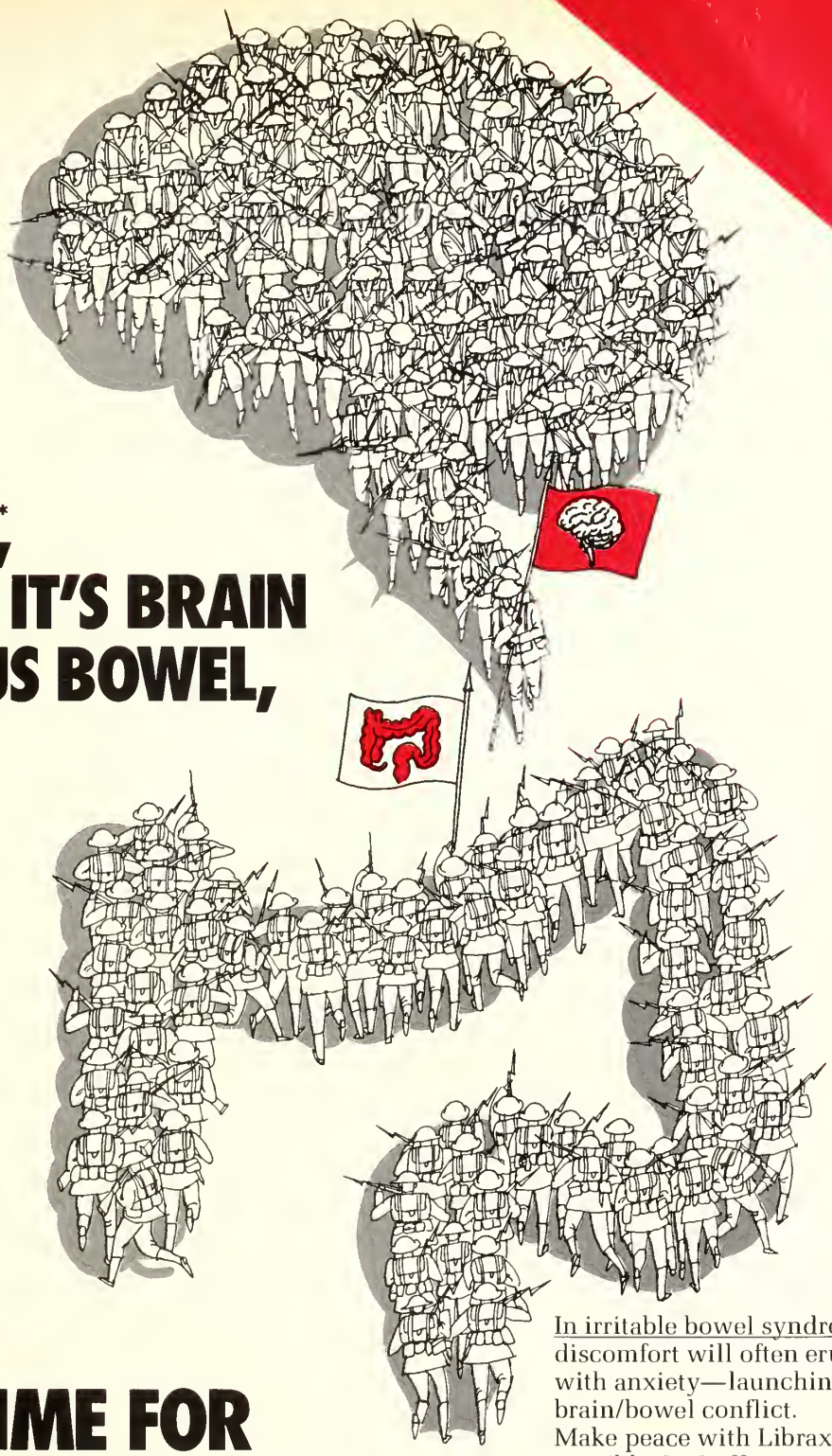

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(Continued from Page 127)

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(Continued on Page 198)

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Articles

Domestic Violence
Risk Factors and Outcomes

DANIEL C. BERRIOS, MD, MPH, *and* DEBORAH GRADY, MD, MPH, *San Francisco, California*

Domestic violence is a pervasive and frequently unrecognized cause of injury among women. We reviewed data from standardized interviews with 218 women who presented to an emergency department with injuries due to domestic violence. Victims ranged in age from 16 to 66 years and constituted a wide range of socioeconomic and ethnic backgrounds. Domestic violence often resulted in severe injury; 28% of the women interviewed required admission to hospital for injuries, and 13% required major surgical treatment. The typical presentation was injuries to the face, skull, eyes, extremities, and upper torso. A third of the cases involved a weapon, such as a knife, club, or gun. In all, 10% of the victims were pregnant at the time of abuse, and 10% reported that their children had also been abused by the batterer. Most victims (86%) had suffered at least one previous incident of abuse, and about 40% had previously required medical care for abuse. Victim recognition and referral to appropriate agencies could be improved if primary care physicians were more aware of the prevalence, severity, frequency of occurrence, and typical presentation of domestic violence.

(Berrios DC, Grady D: Domestic violence—Risk factors and outcomes. West J Med 1991 Aug; 155:133-135)

Domestic violence, specifically abuse by an intimate partner, is a pervasive and frequently unrecognized cause of acute and chronic illness among women. Population-based studies suggest that some form of violence occurs each year in 16% of relationships, and in 6% it is severe—such as punching, kicking, biting, beating, and attacks with a gun or knife.[1] In California, domestic disputes cause one of every three homicide deaths among women (Federal Bureau of Investigation, Uniform Crime Reports, 1982). Injuries due to domestic violence place an enormous strain on health care resources, accounting for an estimated 20% of all emergency department visits by women[2] and 29% of all suicide attempts by women.[3] Domestic violence also burdens community service agencies, with as many as 41% of all assault-related calls to the police attributable to domestic disputes (compilation of San Francisco Police Department dispatch records by the San Francisco Family Violence Project, 1981).

Little information is currently available to differentiate those at high risk for injury due to domestic violence and to guide medical and legal professionals and social scientists in designing effective intervention strategies. Only a few reports have appeared in the medical literature, primarily studies of small numbers of victims of severe abuse[4-9] or questionnaire surveys designed to estimate the prevalence of abuse.[1] Much of the published information on risk factors for and outcomes of domestic violence is based on reviews of emergency department records and evaluations of unconfirmed ("probable" or "suggestive") cases of domestic violence.[2,10]

To describe the risk factors for and outcomes of domestic violence, we analyzed data from standardized interviews with 218 victims of domestic violence who sought assistance from the Emergency Department at the San Francisco (California) General Hospital Medical Center. These records, obtained by the staff of the San Francisco Family Violence Project, provide detailed, objective, and uniform information on a large number of cases of domestic violence.

Methods

Since 1983, all women who presented for medical care at the San Francisco General Hospital Medical Center with a chief complaint of injury as a result of domestic violence or who reported to hospital staff that they were victims of domestic violence have been referred to the San Francisco Family Violence Project, an agency established to provide social, legal, and psychological support to victims of domestic violence. The staff of the Family Violence Project completed standardized data forms during structured personal inter-

TABLE 1.—*Age, Race, and Income of Victim (n=218) and Batterer*

Demographics	*Batterer* No.	*Batterer* (%)	*Victim* No.	*Victim* (%)
Age, yr				
16-25	40	(18)	69	(32)
26-35	88	(40)	91	(42)
36-45	42	(19)	31	(14)
46-55	15	(7)	18	(8)
56 or older	9	(4)	4	(2)
Unknown	24	(11)	5	(2)
Race				
Asian/Pacific Islander	21	(10)	31	(14)
Black	91	(42)	82	(38)
Latino/Hispanic	38	(17)	41	(19)
White	28	(13)	51	(23)
Other	6	(3)	5	(2)
Unknown	34	(16)	8	(4)
Income				
Employed			59	(27)
General Assistance/SSI			59	(27)
Unlawful activities			19	(9)
Batterer			16	(7)
Family			2	(1)
Unknown			63	(29)

SSI = Social Security Insurance

From the Department of Epidemiology and Biostatistics, University of California, San Francisco, School of Medicine.

Reprint requests to Daniel C. Berrios, MD, MPH, University of California, San Francisco, Prevention Sciences Group, 74 New Montgomery St, Suite 600, San Francisco, CA 94105.

TABLE 2.—*Type and Duration of Victim-Batterer Relationship*

Type of Relationship	*No.*	*(%)*	*Median Duration in Years (Range)*
Girlfriend, current or former	112	(51)	2.8 (0.1-15.0)
Ex-wife	6	(3)	5.5 (2.0-11.0)
Wife	91	(42)	5.0 (0.2-30.0)
Not recorded	9	(4)	
All	218	(100)	3.0 (0.1-30.0)

TABLE 3.—*Abuse History*

Interview Question	*No.*	*(%)**	*% Not Recorded*
Previous incidents of abuse	187	(86)	3
Requiring medical attention	87	(40)	10
Requiring hospital admission	29	(13)	12
Ever abused while pregnant	66	(30)	11
Ever miscarried due to abuse	11	(5)	16

*Percentages total >100% because some women came under more than 1 category.

views of several hundred victims of domestic violence.* These data describe the victim, the batterer, the victim's children, and the injuries incurred.

A total of 492 records were available for inclusion in the study. Cases in which the record was less than half completed (n = 264) and cases other than men battering women (n = 10) were excluded from the study. Questionnaires were incomplete primarily because the victim declined or was not available to complete the interview. Results are based on the remaining 218 cases. Means, standard deviations, medians, and ranges were calculated using the Statistical Analysis Software package.

Results

The 218 women interviewed ranged in age from 16 to 66 years (median age 29 years, standard deviation 10 years). Both victims and batterers were ethnically heterogeneous, reflecting the ethnically diverse population of San Francisco. About a third of victims were employed and about a third received public assistance. Only 16 women (7%) listed their primary source of financial support as the batterer (Table 1). The age of the assailants ranged from 19 to 72 years (median 31 years, SD 10 years).

In the overwhelming majority of cases, the victim was related to the batterer as a current or former girlfriend (51% of cases) or as wife (42%). The duration of the relationship between the victim and the batterer ranged from 1 month to 30 years, with a median of 3 years (Table 2). At the time of the incident, 67% of the victims were living with the batterer. In 48% of the cases, the batterer was described by the victim as having an alcohol or drug problem, and, in 43% of the cases, alcohol or drug use was reportedly involved in the index episode of abuse.

For the vast majority of the victims, the incident was not the first episode of abuse in their relationship. At least one previous episode of abuse was reported by 86% of the victims, 40% had required medical attention for abuse in the past, and 13% had required hospital admission for previous abuse. In addition, 10% of the victims reported that they were pregnant at the time of abuse, 30% reported that they had been abused during a previous pregnancy, and 5% stated that they had miscarried because of abuse; 16% of the victims reported that they had attempted suicide (Table 3).

Of all women interviewed, 28% were admitted to hospital for treatment of injuries, and 13% underwent major surgical intervention. Victims frequently required radiographic studies (41%), stitches or casting (25%), and medications (27%). Some had loss of consciousness (11%) or permanent injury (disfigurement, hearing loss, or visual impairment; 5%) resulting from the abusive episode. In addition to bruises (70%), the victims frequently suffered lacerations (39%), choking or strangulation (23%), musculoskeletal injuries (such as bone fractures, tendon or ligament injuries, or joint dislocations; 25%), and internal injuries (13%) (Table 4). Frequently assaulted areas of the body included the face, skull, eyes, upper trunk, and extremities (Table 5). A third of the cases involved a weapon, such as a knife, club, or gun (Table 6).

In 51% of the cases of violence studied, children lived in the household where the violence took place; in 35%, one or more children had witnessed the abuse. In 10%, the victims reported that their children were also abused by the batterer.

Discussion

In the past, attempts to describe domestic violence have used unstructured interviews with victims or medical record reviews of suspected cases. We have presented data documenting incidents of domestic violence among 218 victims through structured interviews on standardized forms, thus minimizing observer bias and the interpretation of responses. Information on half of the eligible cases was not sufficiently complete for inclusion in the study. The effect of this selection bias is uncertain; the most severe cases may have been preferentially documented, or, alternatively, severely abused women may have been too ill or fearful to give full information.

TABLE 4.—*Types of Injury*

Injury	*No.*	*(%)**	*% Not Recorded*
Bruises	152	(70)	13
Laceration	86	(39)	3
Musculoskeletal injury	54	(25)	4
Choking	49	(23)	4
Internal injuries	29	(13)	5
Loss of consciousness	23	(11)	22
Permanent injury	10	(5)	22
Burn or scald	3	(1)	4

*Percentages total >100% because some women had more than 1 type of injury.

TABLE 5.—*Location of Injury*

Location	*No.*	*(%)**
Face	149	(68)
Extremities	107	(49)
Skull	104	(48)
Eyes	97	(45)
Chest, ribs, upper back	97	(45)
Abdomen, pelvis, lower back	42	(19)
Sexual assault	25	(12)
Neck	12	(6)

*Percentages total >100% because some women had injuries in more than 1 location.

*The staff of the San Francisco Family Violence Project collected the data on which this study is based. Ms Debbie Lee, Senior Program Specialist, and Ms Esta Soler, Executive Director, advised and assisted in this study.

TABLE 6.—*Weapons Used During the Abuse Episode*

Weapon	*No.*	*(%)*
Household object	29	(13)
Knife	23	(11)
Stick or club	15	(7)
Gun	4	(2)
Other	1	(0.5)

Our findings indicate that the victims of domestic violence represent all major racial groups and range widely in age. Compared with previous studies,[2,4,9] a considerably larger proportion of victims in this study were nonwhite (77%), but the proportion of women seen in the Emergency Department of San Francisco General Hospital Medical Center who are nonwhite is also high (73%). Abuse occurred among women of all races, and the possibility of domestic violence as the cause of injury in women should be considered, regardless of ethnic background or age.

Several authors have suggested that battered women may remain in an abusive relationship because of financial dependence on the batterer.[2,11] In our study, only 7% of victims were dependent solely on their attacker for financial support. About a third of victims were employed and thus had some financial ability to leave such a relationship. This suggests that for some women, other reasons, such as fear of injury or psychological dependence, deter them from leaving an abusive relationship.

Most intervention efforts are aimed at separating an abused woman from her batterer. Physical separation from the batterer, however, did not ensure protection for our subjects. Fully a third of the victims in our study were not living with their assailants at the time of the index episode, suggesting that victims of domestic violence need better police and judicial protection after leaving the abusive relationship.

Domestic violence is a source of considerable morbidity—28% of our victims were admitted to hospital for their index injury, and 13% required major surgical treatment. In addition, our results and those of previous studies[2,9,10] suggest that the number of abuse episodes may increase during pregnancy. Emergency department personnel and primary care providers should be aware of this association and inquire about domestic violence in pregnant women with injuries. Child abuse by the batterer was commonly reported in our study, suggesting that medical providers should also inquire about child abuse in this setting.

Our findings confirm reports that domestic violence is a recurrent problem.[2,11] In our study, 86% of the victims had been abused before, and almost 40% had previously required medical attention for abuse. Women who are victims of repeated violence in the home may go on to have chronic medical and psychological disorders, such as depression or alcohol and drug abuse. These chronic problems are usually the final stage in a syndrome of battering, preceded by numerous presentations for the medical treatment of injuries; outpatient clinic visits for vague complaints; and labeling as a neurotic, hysteric, or hypochondriac.[10] While no confirmatory data exist, an early recognition of the battering syndrome might decrease the incidence of these associated chronic conditions.

Even though it can result in catastrophic medical and social outcomes, domestic violence is frequently unrecognized or viewed as a "private" event by health professionals. Investigators have used medical record reviews to show that many cases of domestic violence are not recognized by medical providers.[1,12] Instituting victim recognition protocols in emergency departments has yielded significant increases (from 180% to 500%) in the detection of cases of battering and has consistently resulted in increased use of supportive services by battered women.[2,6,10,12]

Primary care physicians and emergency department personnel should consider the possibility of abuse in any woman presenting with bruises or lacerations of the head, extremities, or upper torso, especially those who have sustained such injuries previously. Health care workers should also suspect abuse in cases of pregnant women who are injured and women with injuries who are mothers of abused children. Anyone who wishes to learn more about local services available for victims of domestic violence can call the toll-free, nationwide, 24-hour domestic violence hotline, 800-333-7233 (telecommunications device for the deaf, 800-873-6363). Hospital protocols for providing services to victims of domestic violence can be obtained by writing to the San Francisco Family Violence Project, 1001 Potrero Avenue, Building 1, Suite 200, San Francisco, CA 94110.

The magnitude of the problem of domestic violence in our society and the severity of the injuries incurred argue strongly for its inclusion as a topic of study in medical school curricula, as well as for the implementation of hospital and outpatient protocols aimed at the identification and treatment of its victims. Diagnostic sensitivity and the referral of victims to appropriate agencies will be greatly improved if primary care physicians become more aware of the prevalence of domestic violence and more alert to its risk factors.

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Articles

The Incidence of *Chlamydia pneumoniae* Lower Respiratory Tract Infections Among University Students in Northern California

DEBRA K. KATZMAN, MD, ANN C. TIPTON, MD, *and* IRIS F. LITT, MD, *Stanford;* IRA M. FRIEDMAN, MD, *San Francisco;*
RICHARD W. EMMONS, MD, PhD, *Berkeley; and* JULIUS SCHACHTER, PhD, *San Francisco, California*

Chlamydia pneumoniae has recently been identified as a cause of lower respiratory tract infections. From March 1987 to March 1988, 259 university students—151 students with lower respiratory tract infections and 108 controls—from the University of California, Berkeley, were studied to determine the incidence and pattern of *C pneumoniae* lower respiratory tract infections. Serologic evidence of a recent *C pneumoniae* infection was found in less than 2%, and the organism was not isolated from any of the subjects. Despite the paucity of evidence of a recent infection, 47.5% of this university population showed serologic evidence of a previous *C pneumoniae* infection. The lower incidence of *C pneumoniae* infection in our population, when compared with previous reports, suggests that there may be geographic and temporal differences or fluctuations among populations.

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Chlamydia pneumoniae, a new species within the genus *Chlamydia*, has recently been identified as a cause of acute respiratory tract infection including pneumonia.[1-6] The organism was originally called TWAR after the laboratory designation of two early isolates, TW 183 and AR 39. TWAR strains had been tentatively classified as *Chlamydia psittaci* based on their inclusion morphology in HeLa cells and because of their failure to stain with iodine.[6-8] In a study at the University of Washington (Seattle) from 1984 through 1986, the TWAR organism was identified in 8 of 13 students with pneumonia who had serologic evidence of TWAR infection. This study was particularly important because the recovery of the TWAR organism reduced the likelihood that the serologic findings reflected polyclonal stimulation or cross-reactive antigens from other bacteria. Thus, the study helped establish the etiologic role of TWAR in acute respiratory tract disease.[1]

Seroepidemiologic studies have provided evidence that *C pneumoniae* causes human infection more often than any other chlamydia, including all *Chlamydia trachomatis* serovars. *C pneumoniae* antibody has been found in 25% to 50% of adults in eight different areas of the world.[1-6,9-12] *C pneumoniae* antibody is infrequently found in children younger than 5 years, and the prevalence increases sharply during the ages of 10 to 30 years and persists into old age.[1,13-17]

In this article we report the results of a prospective, cross-sectional, descriptive study designed to determine the incidence and pattern of *C pneumoniae* lower respiratory tract infections in a university population.

Subjects and Methods

Subjects

All subjects were students at the University of California, Berkeley, between the ages of 18 and 35 years who were seen at the Student Health Service from March 1987 to March 1988. Two groups of subjects were studied. The "symptomatic" group included those subjects who had lower respiratory tract illness defined by one of the following criteria: cough, shortness of breath, chest pain, breathing fast, or hoarseness. The "asymptomatic" group included subjects who were seen at the same general medical clinic as the symptomatic subjects and presented with a variety of acute medical complaints. The asymptomatic group served as controls because they had not had a febrile or respiratory illness within the past two weeks. Students were excluded if they had received antibiotics within the previous three weeks. The symptomatic and asymptomatic groups were enrolled simultaneously throughout the year.

Power calculations were carried out to determine the necessary sample size. With a power of 0.9 and a predicted 10% difference in prevalence of *C pneumoniae* between the symptomatic and asymptomatic groups (15% versus 5%, respectively), 200 subjects would be required in each group.

Institutional approval regarding the participation of human subjects was obtained. Informed consent was obtained before enrollment in the study. A self-administered questionnaire was completed and a physical examination was done on each symptomatic patient.

Specimens

Three specimens from the posterior oropharynx were obtained from each symptomatic subject. One specimen was placed in chlamydia collection medium.[18] The second specimen was placed in viral transport medium,[19] and the third was smeared on a microscopy slide and fixed for the Ortho Chlamydia Direct Detection fluorescent-antibody collection kit. This method uses a fluorescein-conjugated monoclonal antibody to a genus-specific chlamydial antigen for detecting chlamydial elementary bodies.[20]

From the Department of Pediatrics, Division of Adolescent Medicine, Stanford University School of Medicine (Drs Katzman, Tipton, and Litt) and Children's Hospital at Stanford (Drs Tipton and Litt), Stanford, California; Departments of Pediatrics (Dr Friedman), Epidemiology and Biostatistics, and Laboratory Medicine (Dr Schachter), University of California, San Francisco, School of Medicine; and the Viral and Rickettsial Disease Laboratory, Division of Laboratories, California Department of Health Services, Berkeley (Dr Emmons). Dr Katzman is a Robert Wood Johnson General Pediatrics Academic Development Fellow at Stanford and is now at the Hospital for Sick Children, Toronto, Ontario.

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Reprint requests to Debra K. Katzman, MD, Hospital for Sick Children, Division of Adolescent Medicine, 555 University Ave, Toronto, Ontario, Canada M5G 1X8.

A single swab of the posterior oropharynx was obtained from each asymptomatic subject and placed in chlamydia collection medium.[18]

Cultures for *C trachomatis* of specimens from the cervix and male urethra were not done.

Serology

Serum specimens of the acute and convalescent phases were drawn four weeks apart. Attempts were made to obtain both serum specimens from all patients. The microimmunofluorescence test[21] with immunoglobulin (Ig) M and IgG conjugates[22] was used for both the acute and convalescent serum. The antigens used included elementary bodies of all 15 *C trachomatis* serovars[23] and the *C pneumoniae* strain TW183. Serologic evidence of a recent infection was defined as a fourfold rise in antibody titer or a titer of 1:32 or greater in the IgM serum fraction. Serologic evidence of a previous infection was defined as a titer that was greater than 1:16 in the IgG serum fraction.

Isolation

Chlamydia pneumoniae *and* Chlamydia trachomatis. All specimens were processed in a cycloheximide-treated McCoy cell system.[24] A blind passage was done four days after inoculation. Cover slips for both passages were assessed for inclusions using a genus-specific, fluorescein-conjugated monoclonal antibody. Selected specimens (those from patients with high antibody levels) were also inoculated into HeLa cells and the yolk sac of embryonated hens' eggs and processed using standard procedures for identification of chlamydiae.[18]

Mycoplasma pneumoniae *and respiratory viruses.* Isolation and complement-fixation tests for *Mycoplasma pneumoniae,* influenza viruses A and B, respiratory syncytial virus, adenovirus, Q fever, parainfluenza virus types 1, 2, and 3, and chlamydia were carried out by the Viral and Rickettsial Disease Laboratory, California Department of Health Services, using standard methods.[19]

Results

A total of 259 subjects were recruited, 151 with lower respiratory tract illness and 108 control subjects. The proportion of all students seen at the Student Health Service with respiratory infection during this study period is unknown. About 5% refused enrollment because of time constraints or refusal of venipuncture or both. Of the 259 participants, 96.1% returned for a follow-up titer. Subjects ranged in age from 18 to 35 years, with a mean of 22.2 years (SD = 3.6). The study population was 55.2% men and 44.8% women.

Of the 151 subjects with lower respiratory tract illness, 2 (1.3%) had serologic evidence of an acute or recent *C pneumoniae* infection. The *C pneumoniae* organism was not isolated from either of these patients. There was neither serologic evidence of an acute *C pneumoniae* infection nor positive oropharyngeal cultures in the asymptomatic or control group.

The following reports describe the cases of two patients with serologic evidence of an acute *C pneumoniae* infection.

Case 1

The patient, a 19-year-old woman, sought care in October 1987 because of a sore throat, fever, and cough. The cough began about a month before her visit and was noted to be productive of yellow mucoid sputum. She also had hoarseness and "red eyes." The patient said she did not smoke. She lived in a campus dormitory and had no contact with birds or animals.

TABLE 1.—*Results of Tests on Acute and Convalescent Serum and Oropharyngeal Culture in 2 Patients With Lower Respiratory Tract Illness and Acute* Chlamydia pneumoniae *Antibody*

Patient	Chlamydia pneumoniae Antibody IgM ocu/con*	Chlamydia pneumoniae Antibody IgG ocu/con*	Culture Results	Antibody to Other Etiologic Agents
1	>256/64	128/128	Negative	None
2	0/128	128/>256	Negative	None

*Acute titer versus convalescent titer.

On physical examination, her vital signs were stable and she was afebrile. The conjunctival linings of both eyelids were red and injected. There was slight tearing without mucopurulent discharge. Her pharynx was erythematous with a small amount of exudate on the right tonsil. She had an occasional expiratory wheeze on auscultation. Her leukocyte and differential counts were normal. No chest radiograph was taken. The patient was treated with a regimen of 1 gram per day of erythromycin ethylsuccinate for 10 days, returned for her repeat serum specimen 34 days after her initial visit, and was subsequently lost to follow-up.

Case 2

The patient, a 25-year-old woman, was seen in November 1987 because of fever, sore throat, hoarseness, and cough for six days. Her cough was productive of clear mucus. A few days before her visit to the Student Health Service, shortness of breath developed. The patient said she did not smoke cigarettes. She shared an apartment with other students, all of whom were healthy. This patient did not have pets or work with animals.

On physical examination, her vital signs were stable and she was afebrile. Her voice was hoarse. The conjunctival linings of both eyelids were red and injected but without discharge. On auscultation there were diffuse rhonchi throughout the bases of both lung fields. The findings of the examination were otherwise entirely normal. A chest radiograph and blood work were not done, and a regimen of doxycycline hyclate, 100 mg twice a day for seven days, was started. She returned for her second serum specimen 27 days after her initial visit. No follow-up was documented.

The results of both of these patients' oropharyngeal cultures and the acute and convalescent serum specimen values to *C pneumoniae* antibody are shown in Table 1. Both patients were from the symptomatic group. No other etiologic agent was identified in either case.

This university study population included 123 subjects (47.5%) with IgG antibodies to *C pneumoniae*. Of these, 74 (49.0%) were from the symptomatic group and 49 (45.4%) were from the control group. Antibody to *C pneumoniae* was slightly more common among men (49.7%) than women (44.8%) (Table 2). The *C pneumoniae* organism was not isolated from any of the subjects. Similarly, all the oropharyngeal specimens tested with the direct fluorescent antibody stain for *C pneumoniae* had negative results.

Evidence of antibody to *C trachomatis* was found in one subject, a 35-year-old woman, in the acute-phase serum. An

TABLE 2.—*Results of the Microimmunofluorescent Antibody Test With* Chlamydia pneumoniae *and* Chlamydia trachomatis *Antigens in 259 University Students*

Antibody	No. of Patients (%) Symptomatic, n = 151	Asymptomatic, n = 108	Men, n = 143	Women, n = 116
C pneumoniae				
Acute	2 (1.3)	0	0	2 (1.7)
Chronic	74 (49.0)	49 (45.4)	71 (49.7)	52 (44.8)
C trachomatis				
Acute	1 (0.66)	0	0	1 (0.9)
Chronic	45 (29.0)	30 (27.8)	32 (23.4)	43 (37.1)

IgG antibody to *C trachomatis* was found in 75 (28.9%) participants, 45 of them from the symptomatic group. There were 32 (42.7%) men and 43 (57.3%) women with IgG antibody to *C trachomatis*. This organism, however, was not isolated from the oropharynx of any of the 259 subjects.

The results of the microimmunofluorescent antibody test with *C pneumoniae* and *C trachomatis* antigens are shown in Table 2.

The results of all studies for the respiratory viruses *M pneumoniae* and *C pneumoniae* in the symptomatic subjects are shown in Table 3. There were 31 (20.5%) symptomatic subjects who had an identifiable cause for their lower respiratory tract illness. No patient had evidence of infection with more than one organism. *M pneumoniae* occurred throughout the study period. The seven cases of influenza B virus occurred in February and March 1988. Because of this high incidence, we decided to run the complement fixation serologic test for influenza B virus on the specimens of all control subjects who enrolled in the study during this time. There was no serologic evidence of recent infection due to influenza B virus in the control group.

TABLE 3.—*Loborotory Results of 151 Subjects With Lower Respirotory Tract Illness*

Etiologic Agent	No. of Subjects, n = 151	Diognostic Tests*
Mycoplosmo pneumoniae	11	Serology
Influenza B	3	Serology and Culture
	2	Culture
	2	Serology
Parainfluenza type 2	2	Culture
Respiratory syncytial virus	2	Serology
Parainfluenza type 1	1	Culture
Influenza A	1	Serology
Adenovirus	1	Serology
Herpesvirus simplex type 1	1	Culture
Rhinovirus		
type 13	1	Culture
type 41	1	Culture
type 71	1	Culture
Chlamydia pneumoniae	2	Serology
Total	31	

*All serologic tests done by complement fixation.

Discussion

Lower respiratory tract disease caused by *Chlamydia pneumoniae* has been shown to occur in endemic or sporadic patterns, and reports on military and civilian populations have suggested that *C pneumoniae* may have both a low background rate of endemic infection and a cyclic epidemic pattern.[1-6,9,10] Kleemola and colleagues reported on four epidemics of pneumonia in military trainees in Finland from 1957 to 1985.[4] The pneumonia attack rate was similar in all four epidemics, ranging from 60 to 84 per 1,000 men. Each epidemic lasted five to seven months, and they occurred during all seasons of the year.[4] During civilian epidemics, 49% to 71% of patients with pneumonia having positive complement fixation tests and thought to have psittacosis actually showed evidence of current *C pneumoniae* infection, compared with only 10% to 20% in nonepidemic years.[6] It is unwise to assume that this is the case in all populations and geographic areas, however. In a study of Seattle college students, approximately 20% of patients with pneumonia had evidence of *C pneumoniae* infection.[1]

Based on this and the Scandinavian reports,[6] this organism would be expected to be a common cause of pneumonia. This certainly was not the case in our study. Only two subjects with lower respiratory tract illness had serologic evidence of a recent *C pneumoniae* infection. In neither did the organism grow in culture. We did find a high seroprevalence of antibody to *C pneumoniae* despite the paucity of evidence of recent infection. This raises the possibility of a cyclic pattern of infectivity for this organism. One of the limitations of this study is that we observed this population only over a year. Evidence for the cyclic nature of *C pneumoniae* infection would probably be much stronger had we been able to continue this study over several years.

Studies of the antibody response in isolation-proven *C pneumoniae* infection have shown that the timing of serum specimens is critical to the serologic diagnosis of *C pneumoniae* infection. Two patterns of antibody response to the *C pneumoniae* organism have been reported. That seen in younger patients consists of a diagnostic titer in the IgM serum fraction that appears after three weeks from the start of symptoms. The IgG response in this group usually does not appear before six weeks from the occurrence of symptoms. The second pattern of antibody response is seen in older persons and is presumed to be associated with secondary infection or reinfection with *C pneumoniae*. An antibody response to *C pneumoniae* in the IgG fraction appears much sooner. If the IgM fraction is positive, it tends to be at a low titer (32 or 64).[3] We attempted to obtain all our follow-up titers at four weeks from the initial visit. The time span between the acute and convalescent titers in this study ranged between 20 and 103 days. The mode and median number of days were 28 and 29, respectively. Some change in IgG antibody may have been missed because patients had their convalescent serum specimen drawn earlier than six weeks.

Previous reports have concluded that respiratory infection with *C pneumoniae* in ambulatory adolescents and young adults is a poorly recognized clinical disorder,[3,5,25,26] probably because of its mild and nonspecific clinical presentation. The infection may be completely asymptomatic.[25] The clinical features of the two persons with serologic evidence of acute *C pneumoniae* infection in this study were those of a mild lower respiratory tract infection. In the study by Grayston and associates, pneumonia associated with *C pneumoniae* was described as being clinically similar to that caused by *Mycoplasma pneumoniae*.[1] In fact, infection with *C pneumoniae* has been described as an atypical pneumonia perhaps mistakenly treated as *M pneumoniae*.[1] In the Scandinavian epidemic of 1981 to 1983, it appeared that those with

TWAR antibody titers suggestive of current infection had diagnoses similar to those without the antibody.[6] During the Finnish pneumonia epidemic caused by *C pneumoniae*, the conscripts had relatively mild illnesses and none were reported to be life-threatening.[4] It now seems possible that in these studies, much of the lower respiratory tract illness ascribed to other respiratory pathogens was actually due to *C pneumoniae*. Furthermore, it is likely that subclinical infections are caused by this organism, as are other chlamydial infections.[27] The asymptomatic group in our study, however, had no evidence of acute *C pneumoniae* infection.

C pneumoniae is a difficult organism to culture. Meticulous care with suitable equipment was taken during all stages of obtaining and transporting specimens. Recent reports have suggested that nasopharyngeal specimens and identification of *C pneumoniae* is a better technique than taking oropharyngeal specimens, as used in this investigation.[28] Furthermore, HL cells have been shown to be an excellent cell culture system for laboratory propagation of *C pneumoniae* when compared with other cell lines (such as McCoy, HeLa-229, or BHK-21) and may also be a more sensitive cell line for the initial identification.[29]

In our study population, *C pneumoniae* antibody was more common than antibody to *Chlamydia trachomatis*. Furthermore, the *C pneumoniae* antibody was slightly more common in men than in women (Table 2). Antibody to *C trachomatis*, on the other hand, was more common in women. These findings have been reported in other populations.[1,3,13]

C trachomatis is known to be a respiratory tract pathogen in children younger than 6 months and in immunocompromised hosts.[30,31] Earlier serologic studies found an association of community-acquired pneumonia and pharyngitis with *C trachomatis*, but there were no attempts to isolate *C trachomatis* from the oropharynx in any of the subjects in these studies.[32,33] It appears that some of the serologic results indicating *C trachomatis* involvement in pneumonia or pharyngitis might in fact reflect *C pneumoniae* antibody. We have found that many (but not all) of the seropositive cases represent cross-reactivity with *C pneumoniae* antigens and probably represent infection with *C pneumoniae*, rather than with *C trachomatis*.[34] At the time of the study by Komaroff and coworkers, *C pneumoniae* had not been identified. Our study, however, found no evidence that *C trachomatis* causes lower respiratory tract infections. *C trachomatis* was not identified in the oropharyngeal specimens from any of the subjects. Although studies have found that *C trachomatis* can cause 3.5% to 6.3% of pharyngitis cases in the adult population,[35,36] *C pneumoniae* is probably a more common cause of pharyngitis. Only 1 of our 259 subjects had serologic results suggestive of a recent *C trachomatis* infection. This 35-year-old woman was contacted and subsequently referred to her physician for follow-up and treatment.

There is still much to learn about the *C pneumoniae* organism. The epidemiology and annual changes in occurrence of *C pneumoniae* are still poorly understood. Further studies and better diagnostic techniques will help determine the clinical spectrum and the epidemiology of this infection.

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Articles

Student Perceptions of Mistreatment and Harassment During Medical School

A Survey of Ten United States Schools

DE WITT C. BALDWIN, Jr, MD; STEVEN R. DAUGHERTY, PhD; *and* EDWARD J. ECKENFELS, *Chicago, Illinois*

Senior students at 10 medical schools in the United States responded to a questionnaire that asked how often, if ever, they perceived themselves being mistreated or harassed during the course of their medical education. Results show that perceived mistreatment most often took the form of public humiliation (86.7%), although someone else taking credit for one's work (53.5%), being threatened with unfair grades (34.8%), and threatened with physical harm (26.4%) were also reported. Students also reported high rates of sexual harassment (55%) and pervasive negative comments about entering a career in medicine (91%). Residents and attending physicians were cited most frequently as sources of this mistreatment. With the exception of more reports of sexual harassment from women students, perceived mistreatment did not differ significantly across variables such as age, sex, religion, marital status, or having a physician parent. Scores from the 10 schools also did not vary significantly, although the presence of a larger percentage of women in the class appeared to increase overall reports of mistreatment from both sexes.

(Baldwin DC Jr, Daugherty SR, Eckenfels EJ: Student perceptions of mistreatment and harassment during medical school—A survey of ten United States schools. West J Med 1991 Aug; 155:140-145)

Medical training has long been considered arduous and stressful. In the past, this often was considered a normal, if not essential, part of an educational process designed to prepare physicians for a difficult and demanding career. Both society and medical education have changed greatly over the years, and there are dramatic differences in the students currently entering medicine.[1] Women, minorities, and older students now constitute a substantial percentage of each class.[2,3] In light of these changes, there is a need to critically reexamine the reaction of students to their medical education experience.

Over the years, research on medical students has shifted from sociologic studies of the educational process, such as Becker and colleagues' *Boys in White: Student Culture in Medical School*, to reports of students' psychological reactions to or ability to cope with the process.[4] Recent work has focused on students' responses to the stress of their medical school experience, emphasizing symptoms such as anxiety, depression, dysphoria, anger, and suicide.[5-8] In general, these reports have implicated individual vulnerabilities and have suggested that certain students or groups of students are at greater risk.[9,10]

During the 1980s, several articulate medical students wrote vividly about their experiences, documenting feelings of humiliation, dehumanization, rejection, and alienation during their education.[11-13] In an analysis of four of these "insider" accounts, Conrad found that all struggled to learn medicine and, at the same time, maintain a humanistic, compassionate perspective.[14] Especially poignant were these students' concerns that eventually they would be "brainwashed" into becoming exactly like those who they felt had tormented them. Equally alarming were their reports of experiences they perceived to be unethical or otherwise offensive and in which they were required to participate because of their subordinate position.

In 1982, Silver commented on the dysphoric reactions of medical students to the stressful environment of medical school.[15] In so doing, he used the word "abuse" to describe how the students were treated, drawing a suggestive parallel with child abuse. Similar signs included progressive apathy and depression in the subjects, possible long-term consequences stemming from such experiences, and incredulity and denial of such abuse by authority figures in the field. No data were presented at that time, but two years later Rosenberg and Silver published an article that included anecdotal data supporting the possibility of such a phenomenon.[16]

In December 1987, we designed and administered a questionnaire to third- and fourth-year medical students at a Midwestern medical school.[17] This pilot survey confirmed Silver's contention that medical students often are subjected to various forms of verbal harassment, including humiliation and belittlement, and are the victims of crude and insensitive remarks, primarily from residents and attending faculty. While few students reported outright physical abuse, complaints of sexual harassment, especially from residents, were relatively common. Examples included "passes in the on-call room," "unfair treatment due to pregnancy," and "propositions of good grades for sexual favors." Students also indicated that they frequently encountered negative comments about their choice of a career in medicine.

To further study the problem and to be able to generalize beyond these preliminary findings, we revised the questionnaire to include questions across a broad range of possible experiences of perceived mistreatment and harassment. The

From the Division of Medical Education Research and Information, American Medical Association (Dr Baldwin); Program Evaluation (Dr Daugherty) and Academic Counseling (Mr Eckenfels), Rush Medical College of Rush University, Chicago, Illinois.

Reprint requests to DeWitt C. Baldwin, Jr, MD, Director, Division of Medical Education Research and Information, American Medical Association, 515 N State St, Chicago, IL 60610.

target population was expanded to include a sample of senior medical students at ten medical schools across the country.

Subjects and Methods

The survey questionnaire was structured to gather information regarding the frequency with which the respondents had experienced different types of perceived mistreatment or harassment over the course of medical school, as well as the source of that perceived mistreatment. Items included being shouted or yelled at; being belittled or humiliated; being assigned tasks for punishment rather than for educational value; having someone take credit for the respondent's work; being physically threatened; being hit, slapped, kicked, or pushed; and being threatened with an unfair grade; as well as experiencing sexual harassment or exploitation and racial and ethnic discrimination. In addition, students were asked how often they had received disparaging remarks concerning their career choice or the practice of medicine, or both.

For each item, respondents were asked to indicate how often this experience had happened specifically to them: never, rarely (one or two times), sometimes (three or four times), or often (five or more times). Finally, students were asked to indicate the source of each type of perceived mistreatment from a list that included classmates, preclinical faculty, clinical faculty, residents or interns, nurses, and patients. Students also were asked to indicate how much the perceived mistreatment bothered them if it did occur and to estimate how often they believed these experiences happened to others at their school.

Subjects

Questionnaires were distributed during the spring of 1988 to fourth-year students at ten medical schools: two each from the Northeast, South, and West and four from the Midwest. Other criteria for school selection included size of the student body (large or small), percentage of women enrolled (high or low), and age of the school (old or new). With the exception of two schools that made mailing lists available, questionnaires were sent to a member of the dean's office, who took responsibility for distribution, either by direct mail or in student mailboxes. All questionnaires were mailed back to the American Medical Association by the respondents, who were provided with stamped, self-addressed envelopes. This was a one-time, self-report survey, with no follow-up possible because all responses were anonymous.

Response

A total of 989 questionnaires were distributed, corresponding to the number of senior students listed at each school. Of this number, 581 fully completed surveys were returned, for a response rate of 59%. Because senior students frequently are absent on residency interviews or elective rotations during their final year, it is not known how many of the questionnaires were actually received, so the effective response rate may have been higher. The average age of the respondents was 27.1 years (SD 3.74). Of those responding, 62% were men. Most (88%) identified themselves as white, with Asians next at 8%.

Results

General Levels of Perceived Mistreatment or Harassment

Nearly all respondents (96.5%) reported experiencing at least one type of perceived mistreatment or harassment from some source at some point during medical school. The bulk of this was of a psychological nature, such as being publicly humiliated or belittled or being shouted or yelled at (Table 1). More than half (55%) reported some form of sexual harassment and at least one instance of someone else taking credit for their work (53.5%). The least frequent category, being hit or pushed, was reported by just over 18% of the sample. In all cases, residents (84.6%) and clinical faculty (79.1%) were reported to be the primary sources of this perceived mistreatment.

TABLE 1.—*Respondents Reporting Some Perceived Mistreatment*

Mistreatment	*Respondents* No.	%
Type		
Shouted and yelled	471	81.2
Publicly humiliated	503	86.7
Tasks for punishment	213	36.7
Take credit	310	53.5
Unfair grade	202	34.8
Threaten with harm	153	26.4
Hit or push	105	18.1
Sexual harassment	319	55.0
Racial harassment	114	19.7
Source*		
Residents	491	84.6
Clinical faculty	459	79.1
Nurses	384	66.2
Patients	345	59.5
Classmates	335	57.7
Preclinical faculty	247	42.6
Total†	581	96.5

*These numbers do *not* include reports of sexual or racial or ethnic mistreatment.
†Number of students reporting at least one incident of perceived mistreatment from any source at any time during medical school.

Of the 26 different items listed in the questionnaire, the modal student indicated some mistreatment on 7 items. Less than 5% responded affirmatively to more than 17 of the items, while only 20 students (3.4%) reported no mistreatment at all.

Frequency of Different Types of Perceived Mistreatment by Source

Table 2 shows the reported frequencies for seven types of perceived mistreatment by source, as well as for negative comments about the students' choice of a medical career. For each listed source except classmates and preclinical faculty, nearly half reported some experience of being shouted or yelled at, although only 4% of the students reported this to be a frequent occurrence. Frequencies for feeling belittled or humiliated were higher. Nearly a third of the students claimed that this happened sometimes or often from residents, clinical faculty, and nurses. Note that while patients appeared to shout or yell at students about as often as residents, students felt considerably less humiliated by this behavior. Apparently students expect this behavior in their care of the sick, although it is perceived as humiliating in the teacher-student relationship.

Reports of academically based mistreatment (tasks for punishment, not being given credit for work, threatened unfairly with a failing grade), were mentioned much less frequently from all sources, with one exception—the house staff. More than 15% of the respondents reported that the assignment of tasks for punishment rather than for educational value or taking credit for their work occurred sometimes or often from residents.

Threats of physical harm and of being slapped, pushed, kicked, or hit were rare. Less than 5% of respondents reported mistreatment of this type from any source except patients, from whom 22% reported some type of physical threat and 11% actual physical abuse. Based on the respondents' marginal comments, most of these incidents occurred while on psychiatric rotations or in the emergency department. The 23 students (4%) who reported being struck by either clinical faculty or residents identified specific incidents on surgery rotations, such as being physically shoved aside or having their hands slapped with instruments while at the operating table.

Disparaging Comments About Medicine and Their Career

Nearly all of the students reported having received negative or disparaging comments about their choice of a medical career or the practice of medicine from at least one source.

TABLE 2.—*Frequency of Perceived Mistreatment by Source*

Perceived Mistreatment/Source	Frequency: Never, %	Rarely, %	Sometimes, %	Often, %
Shouted or yelled at you				
Residents/interns	52.2	27.6	16.0	4.1
Patients	52.2	34.7	10.0	3.1
Nurses	53.4	29.0	13.4	4.1
Clinical faculty	55.3	27.8	12.9	4.0
Classmates	76.0	18.4	4.0	1.6
Preclinical faculty	83.3	14.8	1.6	0.3
Humiliated or belittled you				
Residents/interns	32.4	33.4	24.1	10.0
Clinical faculty	34.0	38.8	19.7	7.6
Nurses	48.6	26.4	17.2	7.8
Classmates	64.0	25.7	7.8	2.6
Preclinical faculty	67.6	25.3	5.7	1.4
Patients	73.6	22.1	2.9	1.4
Assigned tasks for punishment				
Residents/interns	68.3	17.4	9.7	4.7
Clinical faculty	84.5	12.1	2.4	1.0
Nurses	88.8	7.2	2.6	1.4
Preclinical faculty	91.9	7.1	0.5	0.5
Took credit for your work				
Residents/interns	55.3	26.0	14.3	4.3
Classmates	70.7	22.6	5.9	0.9
Clinical faculty	88.3	7.8	2.8	1.2
Nurses	91.0	6.9	1.0	1.0
Preclinical faculty	95.2	3.4	1.2	0.2
Graded unfairly				
Residents/interns	74.0	17.4	7.0	1.6
Clinical faculty	80.4	15.8	2.8	1.1
Preclinical faculty	94.0	5.3	0.4	0.4
Threatened you with harm				
Patients	78.1	17.6	3.3	1.0
Residents/interns	96.4	3.3	0.2	0.2
Clinical faculty	96.7	2.9	0.2	0.2
Classmates	97.7	2.1	0.2	0.0
Nurses	99.0	0.9	0.2	0.0
Preclinical faculty	99.3	0.7	0.0	0.0
Slapped, pushed, or hit you				
Patients	88.7	10.2	0.9	0.2
Clinical faculty	95.7	3.4	0.9	0.0
Residents/interns	96.4	2.2	1.2	0.2
Nurses	98.4	1.4	0.2	0.0
Classmates	98.6	1.4	0.0	0.0
Preclinical faculty	99.5	0.5	0.0	0.0
Made disparaging remarks about medicine				
Residents/interns	24.7	19.3	24.9	31.2
Classmates	29.1	19.3	28.9	22.6
Clinical faculty	32.3	23.2	25.8	18.7
Preclinical faculty	46.0	25.9	18.9	9.3
Nurses	51.8	23.5	14.0	10.7
Family	70.9	19.0	6.4	3.7
Patients	70.9	19.7	6.6	2.6

TABLE 3.—*Mistreatment Indices for Selected Categories by Source of Mistreatment*

Source	Mistreatment Index	Sexual Harassment	Disparaging Comments
Residents/interns	0.166	0.237	0.544
Clinical faculty	0.113	0.208	0.436
Patients	0.114	0.139	0.136
Nurses	0.103	0.090	0.280
Classmates	0.081	0.146	0.482
Preclinical faculty	0.041	0.117	0.302
Family	...	...	0.143

Psychalagical and Physical Mistreatment by Saurce

	Yell	Humiliate	Threaten	Hit
Residents/interns	0.241	0.373	0.015	0.018
Clinical faculty	0.220	0.338	0.014	0.017
Nurses	0.227	0.277	0.005	0.007
Patients	0.214	0.107	0.089	0.042
Classmates	0.102	0.162	0.008	0.004
Preclinical faculty	0.062	0.138	0.002	0.002
Average	0.178	0.233	0.022	0.015

Academic Mistreatment by Saurce

	Tasks as Punishment	Take Credit	Unfair Grading
Residents/interns	0.170	0.225	0.121
Clinical faculty	0.067	0.056	0.082
Nurses	0.058	0.040	...
Preclinical faculty	0.035	0.021	0.025
Classmates	...	0.123	...
Average	0.083	0.093	0.076

More than 65% reported hearing these comments from clinical faculty, and more than 75% indicated receiving them from residents, nearly a third as a frequent occurrence. Such remarks related both to becoming a physician (91%) and the practice of medicine in general (95%). These remarks appeared to have had a notable effect. More than 70% of the students who reported hearing such comments said they were bothered by them.

Computing an Index of Perceived Mistreatment

To make comparisons easier, a series of indices were computed by combining the responses in each category of source and mistreatment type. Such an index combines quantity (number of responses) and frequency (number of occurrences). A high perceived mistreatment index (PMI) would result from either multiple sources and types of mistreatment or a high reported frequency in either of these categories. The highest PMI would result from a combination of multiple sources and high frequency of incidents. Computed in this manner, the PMI provides a gauge of the relative level of perceived mistreatment. The PMI is not a percentage nor a clear statement of frequency but, rather, a simple numeric index useful only for making comparisons between groups. The overall PMI is computed by adding the means of all the mistreatment items, excluding sexual and racial harassment, and dividing by the number of items. Finally, the resulting scores were divided by 3, producing an index ranging between a theoretic low of 0 (no mistreatment) and a high of 1 (mistreatment often, from all sources).

In Table 3, the overall mistreatment index confirms that residents were identified as the chief source of perceived mistreatment, with a figure twice that for classmates and four times that for preclinical faculty. The separate indices for the three categories of mistreatment (psychological, physical, and academic) showed a similar pattern. In almost every

case, the highest score was assigned to residents, with clinical faculty second and preclinical faculty generally the lowest. The single exception to this was reports of greater physical mistreatment from patients.

In addition to permitting comparisons between sources of mistreatment, the PMI also allows comparisons across various types of mistreatment. For example, the index scores for negative or disparaging comments about medicine are noticeably higher than those reported for any other type of perceived mistreatment. Psychological mistreatment is the next most common, with physical mistreatment the lowest, and academic mistreatment falling in the middle.

Comparison Across Demographic Variables

Use of the PMI revealed no significant differences in the reporting of perceived mistreatment in the categories of age, sex, religion, marital status, or having a parent who is a physician (Table 4). Some differences were recorded among the schools in the sample, but these do not achieve statistical significance except for a single school. There were no significant differences in the PMI scores between small and large or new and old schools or between those from different regions of the country. When the PMI scores from each of the sample schools were compared with the percentage of women enrolled in that school, however, the result was a strong linear relation, with a single exception (Figure 1). When that outlier is excluded, the correlation between percentage of women enrolled and reported level of mistreatment is +.89 (n = 9). As seen in Table 4, this is not due to women reporting more mistreatment. It may be that a larger percentage of women in the class either reinforces traditional male-oriented norms and behaviors or else serves to sensitize the entire student body to the existence of mistreatment and discrimination and, therefore, increases its report.[18]

Degree of Effect

The effect of perceived mistreatment on the students was measured by a question after each section asking them to indicate how much the event bothered them. Answers to this question were coded on a 3-point scale: 0, not at all; 1, somewhat; and 2, a lot. Threatening a student with an unfair grade seemed to cause the most concern (mean 1.7), but threats of physical harm bothered respondents the least (0.6). Incidents of belittling and humiliation had the second strongest effect on the medical students (1.3), along with sexual harassment (1.1). The earlier finding that humiliation was

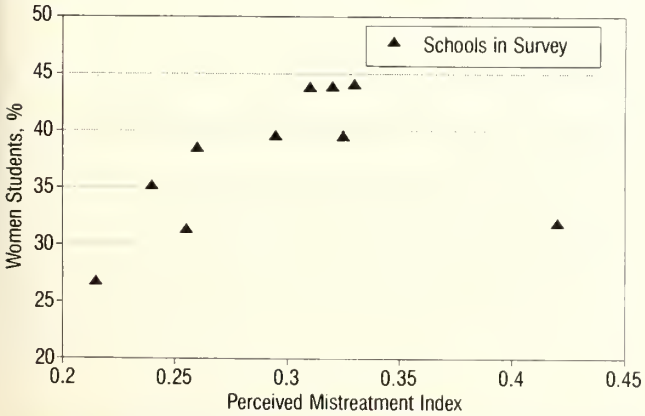

Figure 1.—The perceived mistreatment index is shown by the percentage of women students in the surveyed schools.

TABLE 4.—*Mistreatment Indices for Selected Variables**

Variable	*Means*	*Responses, No.*
Sex		
Men	0.302	361
Women	0.293	219
Age, years		
≤ 25	0.280	280
≥ 26	0.314	295
Religion		
Catholic	0.309	163
Protestant	0.273	169
Jewish	0.305	63
Other	0.337	50
None	0.310	125
Marital status		
Never married	0.296	351
Married	0.291	169
Divorced or separated	0.305	28
Physician parent		
Yes	0.277	102
No	0.304	475
Schools		
1	0.312	41
2	0.254	37
3	0.318	58
4	0.216	44
5	0.418	46
6	0.295	60
7	0.328	77
8	0.239	83
9	0.328	91
10	0.262	44

*Numbers may not always total 581 because of missing responses.

the most frequently cited type of mistreatment, combined with this relatively serious effect on the students, suggests that humiliation may have been the most notable form of harassment experienced by students overall.

Sexual Harassment and Discrimination

Reports of sexual harassment or discrimination differed substantially by the respondent's sex. Table 5 shows that sexual harassment was a fairly common experience for the women students. Just less than half of them indicated some type of harassment from classmates and preclinical faculty, and close to two thirds reported at least one incident involving clinical faculty or residents. Of the women respondents, 30% reported such harassment from these last sources on three or more occasions.

About 25% of men reported some type of sexual harassment from clinical faculty and residents, with 5% stating that this was a frequent occurrence from residents. Marginal comments suggested two general patterns. First, there were reports from gay men who felt discriminated against because of their sexual preferences. Second, many men felt that women were shown favoritism on clerkship rotations, either by men who found them attractive or by women residents who wanted to help them along. The clear finding, however, is that women reported sexual harassment as much as four times more often than did men.

Table 6 gives the distribution of specific kinds of sexual harassment cited by both men and women respondents. For the women, the biggest complaint was of sexist slurs, ranging from being called "Honey" to statements that women were less capable or did not belong in medicine or in a particular specialty. The second most cited area was favoritism in terms of grades or attention. Both men and women respondents felt

TABLE 5.—*Frequency of Sexual Harassment or Discrimination by Source*

Sexual Harassment by Source	Frequency: Never, %	Rarely, %	Sometimes, %	Often, %
Of Men				
Classmates	85.6	8.6	3.3	2.5
Preclinical faculty	85.6	10.3	2.5	1.7
Clinical faculty	76.2	13.6	7.2	2.8
Residents/interns	70.9	16.6	7.5	4.7
Nurses	88.6	6.4	3.9	1.1
Patients	87.8	8.1	3.6	0.6
Of Women				
Classmates	54.4	18.9	20.3	6.5
Preclinical faculty	59.1	26.5	10.7	3.7
Clinical faculty	34.4	34.9	20.9	9.8
Residents/interns	37.8	24.4	24.9	12.9
Nurses	73.1	15.7	6.5	4.6
Patients	47.5	29.5	15.7	7.4

that members of the opposite sex were being given preferential treatment on the basis of their gender.

Only one man and three women reported that they had been directly propositioned for sexual favors. Almost 30% of the women and 5.6% of the men reported encountering some kind of sexual advance, however.

Discussion

The primary objective of our study was to determine whether mistreatment and harassment in medical school is an isolated experience or a widespread perception. Based on a relatively large sample at a variety of schools with differing sizes, locations, and traditions, our findings suggest that the perception of mistreatment exists among most students in a number of medical schools and probably is present in all.

The results confirm Silver's earlier observations[15,16] as well as recent reports from contemporary, single-school studies.[19,20] Nearly all of the medical students in the survey claimed to have experienced some type of mistreatment. This most often took the form of public humiliation, although being threatened with unfair grades and having someone else take credit for one's work also were frequently reported. In addition, high rates of sexual harassment or discrimination were reported. Residents and attending physicians were cited most frequently as the sources of such mistreatment. Combined with reports of pervasive negative comments about medicine as a career from faculty and others, these results suggest that medical education is occurring in an insensitive, occasionally punitive environment, which adds psychological hazing to a taxing curriculum and workload. No comparable studies as yet have been reported on students in other fields.

As with any self-report study, the interpretation of these findings must be guarded. Like pain, mistreatment and harassment are largely subjective experiences that are best known to the subject. Despite the liberal use of examples, the survey instrument gave no precise definition of mistreatment. Responses were left to the interpretation and description of the respondents. Undoubtedly, there are great differences among students in their expectations of the student role and their perceptions of what might be considered mistreatment or harassment.[21] Although this involves a high degree of subjectivity, it is fully consistent with the topic at hand. Students may feel mistreated in different ways depending on the particular situation. Their common experience,

TABLE 6.—*Types of Sexual Harassment by Sex of Respondents*

Sexual Harassment	Men, % n=361	Women, % n=219
Sexist slurs	10.0	61.5
Favoritism	24.2	46.3
Sexual advances	5.6	28.9
Sexist teaching materials	5.4	25.7
Poor evaluations	12.8	24.3
Denied opportunities	9.4	23.4
Malicious gossip	7.5	19.3
Exchange of rewards for sexual favors	0.3	1.4

however, is that some aspects of their education are perceived as abusive.

Concern also can be raised over the response rate of 59%. While such figures are considered acceptable by most opinion survey researchers, it would have been desirable to have had a higher response rate. On the other hand, there were negligible differences between schools with higher and lower response rates with regard to individual items or categories, suggesting that higher response rates probably would have made little difference. Indeed, several recent studies have suggested that higher response rates may not be required in attitudinal surveys when there is reason to think that respondents are not significantly different from nonrespondents.[22,23] Under the conditions of student mobility and absence during the senior year, the response rate of nearly 60% to a lengthy, 11-page questionnaire in the midst of a busy clinical schedule appears valid.

Beyond concerns over the findings of verbal, physical, sexual, and other forms of perceived mistreatment looms the larger issue of what effect such a learning environment may have on students, especially with regard to their future careers as physicians. It would be difficult to see a "kinder and gentler" physician emerging from an environment in which students perceive themselves as having been mistreated or humiliated to the extent revealed in this survey. Of more serious note is the possibility that such attitudes and behaviors may be visited on younger students or even patients. If child abuse is an appropriate analogue, there may be a "transgenerational legacy" that leads to future mistreatment of others on the part of those who have been mistreated as students. The irony of these findings is that these senior medical students will become residents within a few months and are being prepared for a profession in which they will eventually assume positions of considerable authority over future students and their patients.

The question must be raised as to why students have submitted to such mistreatment and harassment for so long without complaining. Recent reports, as well as marginal comments on the survey, speak of the perceived uselessness of such complaints.[19,20] The answer appears to lie in the enormous emotional, intellectual, physical, and economic commitments made by most medical students to their aspirations for a career in medicine. It seems to be both cognitively and emotionally dissonant for students to think that their role models could or would want to mistreat them. This may explain why many older physicians deny such feelings or experiences in their own education and training.

This delivery of power into the hands of faculty and supervisory personnel makes the issue of sexual harassment

difficult to assess and to control. There can be no assurance that a student does not feel somehow pressured or compelled to participate in an activity, however consensual, that carries with it the possible threat of domination and rejection.[24] Judging from the data reported here and elsewhere, it appears that faculty and residents do sexually harass and exploit students and that the latter, more frequently than not, feel aggrieved by the process. This is of even greater concern because of emerging evidence that students who have participated in a sexual relationship with a supervisor during training are more likely later to engage in sexual relationships with patients.[25]

The extraordinarily high number of negative comments reported as being made to medical students concerning their choice of a career in medicine should be of concern to medical school administrators and to organized medicine. The occasional comment of dissatisfaction with job or career training is to be expected and may be a painful but honest perception on the part of residents and faculty. Exposure over several years, however, to denigrating, negative comments about one's chosen profession must surely impair morale and foster uncertainty and self-doubt among students. Such negative comments may further enhance the feelings of mistreatment among medical students, if they are led to believe that they have made a poor career choice in the face of the obvious stresses of medical school.

In conclusion, we have presented data strongly suggesting that some form of mistreatment and harassment during medical school is a part of many students' perceptions and experience. The overriding point may not be the specifics of such mistreatment so much as the effect it may have on students' future attitudes and behavior as physicians. It seems likely that such experiences compromise the learning environment, impair the well-being and emotional development of students, and establish poor modeling of the professional role, all of which may translate into impaired physicians and even impaired patient care. In the words of one of the students, "Good medical training does not have to be humiliating or dehumanizing."

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Conferences and Reviews

A Practical Approach to Acid-Base Disorders

Discussant
RICHARD J. HABER, MD

This discussion was selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from a transcription, it has been edited by Homer A. Boushey, MD, Professor of Medicine, and Nathan M. Bass, MD, PhD, Associate Professor of Medicine, under the direction of Lloyd H. Smith, Jr, MD, Professor of Medicine and Associate Dean in the School of Medicine.

EDITOR'S NOTE: *This discussion of acid-base disorders was presented at Medical Grand Rounds at San Francisco General Hospital Medical Center and impressed the editors as outlining a clinically useful approach to a sometimes complicated subject.*

MERLE A. SANDE, MD*: *Acid-base disturbances are common in patients admitted to our service and are sometimes confusing when three partially offsetting disorders are coincident in the same patient. Recognizing important underlying clinical problems and initiating the proper therapy will be ensured if one combines a simple, disciplined approach to analyzing changes in arterial blood gases and electrolytes with focused correlation with the clinical setting. Richard J. Haber, MD, Chief of the Division of General Internal Medicine at San Francisco General Hospital, reviews his approach to this important topic.*

RICHARD J. HABER, MD†: Because of its reputation for complexity, acid-base analysis intimidates many physicians. In reality, acid-base disturbances obey well-defined biochemical and physiologic rules and are easily recognized and interpreted. In this review I present a practical, stepwise approach to interpreting disturbances in blood gas and electrolyte values. The method is simple and does not require a nomogram or complicated mathematical formulas, yet it will identify clinically important acid-base disorders. I start with simple problems and proceed to more complex abnormalities.

Data Base

Assessing a patient's acid-base status begins with the measurement of the arterial pH, partial pressure of carbon dioxide, and bicarbonate. Blood gas analyzers directly measure the pH and P_{CO_2}. The bicarbonate value is calculated from the Henderson-Hasselbalch equation. A more direct measurement of bicarbonate is obtained from determining the total venous carbon dioxide. Because of the dissociation characteristics of carbonic acid at body pH, dissolved carbon dioxide is almost exclusively in the form of bicarbonate, and, for practical purposes, the total carbon dioxide content is equivalent (± 3 mmol per liter) to the bicarbonate concentration. If a simultaneously determined blood gas bicarbonate value and total venous carbon dioxide content are substantially different, a second measurement is required before analysis can proceed.

Terms and Definitions

Normal values for arterial pH, P_{CO_2}, and bicarbonate and values that define primary acid-base disorders are given in Table 1. If the pH is less than normal (<7.35), the patient is said to be acidemic. If the pH is greater than normal (>7.45), the patient is alkalemic. Note the separate terms for pH to allow for describing the net effect of multiple respiratory or metabolic abnormalities.

If the P_{CO_2} is lower than normal (<35 mm of mercury) and this is a primary process, then a respiratory alkalosis is present. If the P_{CO_2} is higher than normal (>45 mm of mercury) and this is a primary process, then a respiratory acidosis is present. If the P_{CO_2} is abnormal in compensation for a primary metabolic process, the disturbance is described as respiratory compensation—"metabolic acidosis with respiratory compensation," for example.

If the arterial bicarbonate level is less than normal (<22 mmol per liter) and this is a primary abnormality, a metabolic acidosis is present. If the bicarbonate level is higher than normal (>26 mmol per liter) and this is a primary process, a metabolic alkalosis is present. If bicarbonate levels are abnormal in compensation for a primary respiratory abnormality, the disturbance is called metabolic compensation.

Respiratory compensation for metabolic disorders is rapid. Full metabolic compensation for respiratory disturbances requires renal adjustment and takes three to five days.

Simple Acid-Base Disorders

The first step in acid-base analysis is to identify all abnormalities in pH, P_{CO_2}, and bicarbonate. The next is to decide which abnormalities are primary and which are compensatory. Table 2 lists three rules of thumb to help in making this determination.

The first rule directs us to look at the pH. Whichever side of 7.40 the pH is on, the process or processes that caused it to shift to that side are the primary abnormalities. If the pH is lower than 7.40, then an elevated P_{CO_2} (respiratory acidosis) or a lowered bicarbonate (metabolic acidosis) would be pri-

*Professor and Chair, Department of Medicine, San Francisco General Hospital Medical Center, University of California, San Francisco (UCSF), School of Medicine.

†Chief, Division of General Internal Medicine; Assistant Chief, Medical Services, San Francisco General Hospital Medical Center; Professor, Clinical Medicine, UCSF.

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Reprint requests to Homer A. Boushey, MD, Department of Medicine, University of California, San Francisco, School of Medicine, San Francisco, CA 94143.

TABLE 1.—*Primary Acid-Base Disorders*

Variable	*Primary Disorder*	*Normal Range, Arterial Gas*	*Primary Disorder*
pH	Acidemia	←7.35-7.45→	Alkalemia
Pco_2, mm of mercury	Respiratory alkalosis	←35-45→	Respiratory acidosis
Bicarbonate, mmol/liter	Metabolic acidosis	←22-26→	Metabolic alkalosis

TABLE 2.—*Rules of Thumb for Recognizing Primary Acid-Base Disorders Without Using a Nomogram*

Rule 1
Look at the pH. Whichever side of 7.40 the pH is on, the process that caused it to shift to that side is the primary abnormality
Principle: The body does not fully compensate for primary acid-base disorders

Rule 2
Calculate the anion gap. If the anion gap is ≥20 mmol per liter, there is a primary metabolic acidosis regardless of pH or serum bicarbonate concentration
Principle: The body does not generate a large anion gap to compensate for a primary disorder

Rule 3
Calculate the excess anion gap (the total anion gap minus the normal anion gap [12 mmol per liter]) and add this value to the measured bicarbonate concentration; if the sum is greater than a normal serum bicarbonate (>30 mmol per liter), there is an underlying metabolic alkalosis; if the sum is less than a normal bicarbonate (<23 mmol per liter), there is an underlying nonanion gap metabolic acidosis
Principle: 1 mmol of unmeasured acid titrates 1 mmol of bicarbonate (+ Δ anion gap = − Δ [HCO_3^-])

mary abnormalities. If the pH is higher than 7.40, then a lowered Pco_2 (respiratory alkalosis) or a raised bicarbonate (metabolic alkalosis) would be primary.

The pathophysiologic principle behind this rule is that the body does not fully compensate even for chronic acid-base disorders. Over time the pH approaches but does not completely return to normal. This observation allows us to use the direction of pH change to identify the primary disorder.

Respiratory Alkalosis

Consider a patient with a pH of 7.50, a Pco_2 of 29 mm of mercury, and a bicarbonate concentration of 22 mmol per liter. Because the patient is alkalemic, the low Pco_2 is a primary disturbance and a respiratory alkalosis is present. The lack of metabolic compensation—that is, the normal bicarbonate—indicates that the disorder is acute. The causes of acute respiratory alkalosis are listed in Table 3. Why make such a list?

Acid-base disturbances are manifestations of underlying clinical disorders. Identifying a primary acid-base abnormality—in this case, respiratory alkalosis—identifies a disorder caused by only a limited number of disease processes. Establishing a specific diagnosis is clinically important because treatment is best aimed at correcting the underlying cause of the acid-base abnormality rather than at correcting the abnormality per se.

Respiratory Acidosis

What about a patient with a pH of 7.25, a Pco_2 of 60 mm of mercury, and a bicarbonate of 26 mmol per liter? This person is acidemic with an increased Pco_2 and a normal bicarbonate: a respiratory acidosis with no evidence of metabolic compensation. The causes of acute respiratory acidosis are listed in Table 4.

What if the next patient presented with a pH of 7.34, a Pco_2 of 60 mm of mercury, and a bicarbonate of 31 mmol per liter (Table 5)? In this person, both the Pco_2 and the bicarbonate levels are elevated, two abnormalities with opposite effects on pH. Which one is primary and which compensatory? Because the pH is lower than 7.40, the primary disorder is still a respiratory acidosis. The elevated bicarbonate (and near-normal pH) indicates that metabolic compensation has occurred and that the acidosis is chronic.

Differentiating acute from chronic respiratory acidosis has important clinical implications. Acute respiratory acidosis is a medical emergency that may require emergent intubation and mechanical ventilation, whereas chronic respiratory acidosis is often a clinically stable condition. Attention to the pH and bicarbonate values will differentiate acute from chronic hypoventilation.

Metabolic Alkalosis

Assess the following blood gas combination: pH 7.50, Pco_2 48 mm of mercury, and bicarbonate level 36 mmol per liter. Because the patient is alkalemic, the elevated bicarbonate level is the primary abnormality and the patient has a metabolic alkalosis with respiratory compensation. Although the partial carbon dioxide pressure is a powerful respiratory stimulus, it may rise modestly in compensation for a metabolic alkalosis. A Pco_2 in excess of 55 mm of mercury is unlikely to be solely compensatory, however, and an additional primary respiratory abnormality should be sought.[1,2]

TABLE 3.—*Acute Respiratory Alkalosis*

Arterial Gas Value		*Interpretation*
pH	7.50	Alkalemia
Pco_2*	29 mm of mercury	Respiratory alkalosis
HCO_3^-	22 mmol/liter	Normal HCO_3^-
Causes		
Anxiety		
Hypoxia		
Lung disease with or without hypoxia		
Central nervous system disease		
Drug use—salicylates, catecholamines, progesterone		
Pregnancy		
Sepsis		
Hepatic encephalopathy		
Mechanical ventilation		

*This is the primary abnormality.

TABLE 4.—*Acute Respirotory Acidosis*

Arterial Gas Value		*Interpretation*
pH	7.25	Acidemia
Pco_2*	60 mm of mercury	Respiratory acidosis
HCO_3^-	26 mmol/liter	Normal HCO_3^-

Causes
- Central nervous system (CNS) depression—drugs, CNS event
- Neuromuscular disorders—myopathies, neuropathies
- Acute airway obstruction—upper airway, laryngospasm, bronchospasm
- Severe pneumonia or pulmonary edema
- Impaired lung motion—hemothorax, pneumothorax
- Thoracic cage injury—flail chest
- Ventilator dysfunction

*This is the primary abnormality.

The causes of metabolic alkalosis can be divided into those associated with a decreased extracellular volume, or the posthypercapnic state (low urinary chloride level), and those associated with a normal or increased extracellular volume or recent diuretic use (normal or high urinary chloride level), as listed in Table 6. Measuring the urinary chloride level is the preferred method for assessing the renal response to circulating volume in patients with metabolic alkalosis; the urinary sodium concentration is less reliable as a guide, for the renal threshold for bicarbonate may be exceeded and sodium spilled as the bicarbonate cation even in a patient who is volume depleted.

Metabolic Acidosis

Next consider a patient with a pH of 7.20, a Pco_2 of 21 mm of mercury, and a bicarbonate level of 8 mmol per liter. The patient is acidemic; therefore, the low bicarbonate is the primary abnormality and a metabolic acidosis with respiratory compensation is present. To help in distinguishing the cause, metabolic acidoses are commonly divided into those with and those without an anion gap. Because the serum potassium contributes little to the total extracellular electrolyte pool, the anion gap is traditionally calculated by excluding the potassium value and subtracting the sum of the chloride and bicarbonate (total carbon dioxide) levels from the sodium concentration. In the literature, the normal anion gap is reported as 12 ± 2 (mean ± SD) mmol per liter,[3,4] although the normal range may be lower when measured on the newest generation of autoanalyzers.[4] The causes of anion gap and nongap acidosis are listed in Table 7.

Mixed Acid-Base Disorders

In each of the previous examples, we have assumed that only one primary abnormality is present. In real life, however, patients often have more than one disorder.

TABLE 5.—*Chronic Respiratory Acidosis With Metobolic Compensotion*

Arterial Gas Value		*Interpretation*
pH	7.34	
Pco_2*	60 mm of mercury	Respiratory acidosis
HCO_3^-	31 mmol/liter	Metabolic compensation

Causes
- Chronic lung disease—obstructive or restrictive
- Chronic neuromuscular disorders
- Chronic respiratory center depression—central hypoventilation

*This is the primary abnormality.

Mixed acid-base disorders can be identified by determining the expected compensatory response to a given change in the primary abnormality and assuming that any value that falls outside this range represents an additional primary disorder. Such 95% confidence bands are the basis for commonly used nomograms[5] and for the mathematical formulas popularized by Narins and Emmett.[3] Unfortunately, mathematical equations, especially ones that are different for acute and chronic disorders, can be difficult to memorize. Nomograms are simple to use but can further mystify acid-base analysis by providing answers without necessarily requiring an understanding of the relevant pathophysiology. A simpler alternative, which will identify most clinically important disorders, is outlined in Table 2.

We have already discussed the first rule of thumb that directs us to look at the pH to determine which abnormality is primary if more than one abnormality is present. The second rule instructs us to determine the serum electrolyte values—sodium, chloride, and total carbon dioxide—and to calculate the anion gap. If the anion gap is 20 mmol per liter or greater, then a metabolic acidosis is present regardless of the pH or serum bicarbonate concentration.

The physiologic principle behind this assertion is that the body does not generate a large anion gap to compensate even for a chronic alkalosis. Therefore, a substantial increase in unmeasured anions indicates a primary disorder, a metabolic acidosis, regardless of the pH or the bicarbonate concentration. Three lines of evidence support this statement. First, an anion gap of greater than 20 mmol per liter is more than 4 standard deviations from the mean and therefore is unlikely to be due to chance.[3,4] Second, although a modest increase in the anion gap occurs in patients with metabolic or respiratory alkalosis due primarily to an increase in the negative charge of serum proteins, even in severe alkalosis this increase is almost never greater than 20 mmol per liter.[1,6-8] Last, a specific cause for an increased anion gap can be found in fewer than 30% of patients with a gap greater than 12 mmol per liter but less than 20 mmol per liter, as compared with 77% of those with a gap of 20 mmol per liter or greater and all of those with a gap of more than 30 mmol per liter (Table 8).[9] Thus, an anion gap of greater than 20 mmol per liter is highly predictive of the presence of an identifiable metabolic acidosis. The greater the anion gap, the more likely it is that a specific metabolic acidosis will be found.

TABLE 6.—*Metabolic Alkolosis With Respirotory Compensotion*

Arterial Gas Value		*Interpretation*
pH	7.50	Alkalemia
Pco_2	48 mm of mercury	Respiratory compensation
HCO_3^-*	36 mmol/liter	Metabolic alkalosis

Causes

Urinory Chloride Level Low	*Urinory Chloride Level Normol or High*
Vomiting, nasogastric suction	Excess mineralocorticoid activity—Cushing's syndrome, Conn's syndrome, exogenous steroids, licorice ingestion, increased renin states, Bartter's syndrome
Diuretic use in past	Current or recent diuretic use
Posthypercapnia	Excess alkali administration
	Refeeding alkalosis

*This is the primary abnormality.

TABLE 7.—*Metabolic Acidosis With Respiratory Compensation*

Arterial Gas Value		*Interpretation*
pH	7.20	Acidemia
P_{CO_2}	21 mm of mercury	Respiratory compensation
HCO_3^-*	8 mmol/liter	Metabolic acidosis
		Anion gap = sodium − chloride + bicarbonate
		Normal = 12 ± 2 (SD) mmol/liter

Causes

Nonanion Gap	*Anion Gap*
GI bicarbonate loss	Ketoacidosis
Diarrhea	Diabetic
Ureteral diversions	Alcoholic
Renal bicarbonate loss	Renal failure
Renal tubular acidosis	Lactic acidosis
Early renal failure	Rhabdomyolysis
Carbonic anhydrase inhibitors	Toxins
Aldosterone inhibitors	Methanol
Hydrochloric acid administration	Ethylene glycol
Posthypocapnia	Paraldehyde
	Salicylates

GI = gastrointestinal

*This is the primary abnormality.

If the anion gap is increased, then the third rule instructs us to calculate the excess anion gap—the total anion gap minus the normal anion gap (12 mmol per liter)—and add this value to the measured bicarbonate concentration (total venous carbon dioxide content). If the sum of the excess anion gap and the measured bicarbonate is greater than a normal serum bicarbonate concentration (normal range, 23 to 30 mmol per liter), then an underlying metabolic alkalosis is present regardless of the pH or measured bicarbonate value. If the sum is less than a normal bicarbonate concentration, then an underlying nongap metabolic acidosis is present.

The physiologic basis for this statement is that for each millimole of acid titrated by the carbonic acid buffer system, 1 mmol of bicarbonate is lost through conversion to carbon dioxide and water and 1 mmol of the sodium salt of the unmeasured acid is formed. Because each millimolar decrease in bicarbonate is accompanied by a millimolar increase in the anion gap, the sum of the new (excess) anion gap and the remaining (measured) bicarbonate value should be equal to a normal bicarbonate concentration. These relationships are schematically presented in Figure 1. If the sum of the excess anion gap and the measured bicarbonate value exceeds the normal bicarbonate concentration, then an additional disorder (a metabolic alkalosis) has added bicarbonate to the extracellular space. If the sum is less than normal, then an additional process (a nonanion gap metabolic acidosis) has caused gastrointestinal or renal loss of bicarbonate. Published reports indicate that this reciprocal relationship between the increase in anion gap (and organic acid salt) and the decrease in serum bicarbonate concentration is actually observed in uncomplicated organic acidoses[10-18] but that the one-for-one relationship is altered if there is superimposed vomiting[10,19,20] or renal loss of bicarbonate.[15-17] These data suggest that although the body's titration of acid represents a complex interplay of multiple buffering systems, because bicarbonate remains the major extracellular buffer over a wide range of pH,[21] our rule is empirically correct and clinically useful.

TABLE 8.—*The Relation Between Level of Anion Gap and Biochemical Diagnoses in 51 Patients Without Renal Failure**

Anion Gap, mmol/liter	*Patients, No.*	*Biochemically Confirmed Organic Acidosis Present, No.*	*%*
17 - 19	7	2	29
20 - 24	20	13	65
25 - 29	15	12	80
30 - 45	9	9	100
≥20	44	34	77

*Adapted from Gabow et al.9

Respiratory Alkalosis and Metabolic Acidosis

Consider a patient with a pH of 7.50, a P_{CO_2} of 20 mm of mercury, a bicarbonate concentration of 15 mmol per liter, a sodium concentration of 140 mmol per liter, and a chloride level of 103 mmol per liter. This person is alkalemic with a low P_{CO_2} and a low bicarbonate concentration. Because the pH is high, the low P_{CO_2} represents a primary disorder, and a respiratory alkalosis is present. At first inspection, the low bicarbonate level appears to be in metabolic compensation for a chronic alkalosis. Follow the second rule, however, and calculate the anion gap: 140 − (103 + 15) = 22 mmol per liter. A gap of 22 mmol per liter is greater than would be expected solely in compensation for a chronic alkalosis and suggests that a second primary disorder, an anion gap metabolic acidosis, is also present. If the anion gap had not been calculated, the underlying metabolic acidosis would have been missed. Now, proceed to the third rule and calculate the excess anion gap: 22 − 12 = 10 mmol per liter, and add it to the measured bicarbonate level: 15 mmol per liter. The sum, 25 mmol per liter, is normal, indicating that no further pri-

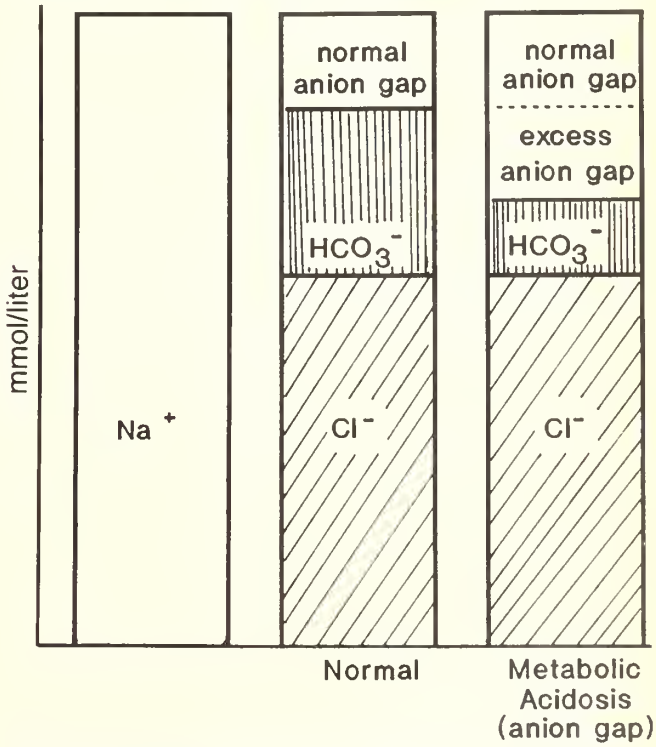

Figure 1.—The graph shows the effect of unmeasured acid on the bicarbonate concentration, anion gap, and excess anion gap. Anion gap = $[Na^+] - ([Cl^-] + [HCO_3^-])$; excess anion gap = total anion gap − normal anion gap (12 mmol/liter).

mary abnormalities are present. This patient had ingested a large quantity of aspirin and displayed the centrally mediated respiratory alkalosis and the anion gap metabolic acidosis associated with salicylate overdose.[22] Respiratory alkalosis and metabolic acidosis, however, can occur together in a variety of related and unrelated clinical conditions (Tables 3 and 7).

Metabolic Acidosis and Metabolic Alkalosis

The following example is adapted from a lecture by Robert Narins, MD: pH 7.40, P_{CO_2} 40 mm of mercury, bicarbonate 24 mmol per liter, sodium 145 mmol per liter, and chloride 100 mmol per liter. This is a seemingly normal set of values until the anion gap is calculated: 145 − (100 + 24) = 21 mmol per liter. The increased gap defines a metabolic acidosis even though the pH is normal. Now calculate the excess anion gap: 21 − 12 = 9 mmol per liter, and add it to the measured bicarbonate: 24 mmol per liter. The sum, 33 mmol per liter, is higher than a normal bicarbonate concentration, indicating a metabolic alkalosis is also present. These laboratory values are from a patient with chronic renal failure (causing the metabolic acidosis) who began vomiting (hence the metabolic alkalosis) as his uremia worsened. The acute alkalosis of vomiting offset the chronic acidosis of renal failure, resulting in a normal pH. Without a systematic approach to acid-base disorders, including calculation of the anion gap and of the excess anion gap, these mixed acid-base disorders could easily have been overlooked.

Respiratory Alkalosis, Metabolic Acidosis, and Metabolic Alkalosis

Analyze the following blood gas and electrolyte values: pH 7.50, P_{CO_2} 20 mm of mercury, bicarbonate 15 mmol per liter, sodium 145 mmol per liter, and chloride 100 mmol per liter. The pH is high, the P_{CO_2} and bicarbonate values are low, and there is an increased anion gap. Because the pH is above 7.40, the low P_{CO_2} is a primary abnormality, and the patient has a respiratory alkalosis. Because the anion gap is elevated (30 mmol per liter), a metabolic acidosis is also present. Because the sum of the excess anion gap (18 mmol per liter) and the measured bicarbonate (15 mmol per liter) is greater than a normal bicarbonate concentration, the patient also has a metabolic alkalosis. The near-normal pH reflects the competing effects of these three primary disorders. This person had a history of vomiting (the metabolic alkalosis), evidence of alcoholic ketoacidosis (causing metabolic acidosis), and findings compatible with a bacterial pneumonia (hence the respiratory alkalosis). These three independent disorders can occur concurrently in other clinical settings (Tables 3, 6, and 7). Four primary acid-base disorders cannot coexist, as a patient cannot hypoventilate and hyperventilate at the same time.

Respiratory Acidosis, Metabolic Acidosis, and Metabolic Alkalosis

What if a patient presents with a pH of 7.10, a P_{CO_2} of 50 mm of mercury, a bicarbonate level of 15 mmol per liter, a sodium level of 145 mmol per liter, and a chloride level of 100 mmol per liter? The person is acidemic with an elevated P_{CO_2}, a lowered bicarbonate, and an increased anion gap (30 mmol per liter). Because the pH is low, the increased P_{CO_2} (respiratory acidosis) and decreased bicarbonate (metabolic acidosis) are both primary disorders. The anion gap is increased; therefore, the metabolic acidosis is of the anion gap variety. Because the sum of the excess anion gap (18 mmol per liter) and the measured bicarbonate (15 mmol per liter) is greater than the normal bicarbonate concentration, a metabolic alkalosis is also present: three primary disorders. This patient presented in an obtunded state (respiratory acidosis), with a history of vomiting (metabolic alkalosis) and laboratory findings consistent with diabetic ketoacidosis (metabolic acidosis).

Interestingly, identical blood gas values could occur in a patient with chronic respiratory acidosis and metabolic compensation in whom an acute anion gap metabolic acidosis developed. Although the pH, P_{CO_2}, and bicarbonate values would be the same in both these patients, clinical correlation would readily differentiate between the two. As is the case for other diagnostic tests, acid-base abnormalities cannot be properly interpreted without knowledge of the clinical context.

Anion Gap and Nonanion Gap Metabolic Acidoses

Consider a patient with the following values: pH 7.15, P_{CO_2} 15 mm of mercury, bicarbonate level 5 mmol per liter, sodium level 140 mmol per liter, and chloride value 110 mmol per liter. The patient is acidemic with a low P_{CO_2}, a low bicarbonate, and an increased anion gap (25 mmol per liter). At first glance, this patient has a simple anion gap metabolic acidosis with respiratory compensation. The sum, however, of the excess anion gap (13 mmol per liter), and the measured bicarbonate (5 mmol per liter) is lower than the normal bicarbonate concentration, suggesting that additional gastrointestinal or renal loss of bicarbonate has occurred and that both an anion gap and a nonanion gap metabolic acidosis are present. Diabetic ketoacidosis was responsible for the anion gap acidosis in this patient. The nonanion gap (hyperchloremic) acidosis is that phenomenon observed in the recovery phase of diabetic ketoacidosis due to failure to regenerate bicarbonate from ketoacids lost in the urine.[15-17] If the sum of the excess anion gap and the measured bicarbonate had not been calculated, the underlying nongap acidosis would not have been appreciated.

Conclusions

Acid-base disturbances are not difficult to analyze if approached in a systematic manner. First, assess the patient's clinical status. A proper interpretation of laboratory results requires knowledge of the clinical setting. Second, determine blood gas values and identify all abnormalities in pH, P_{CO_2}, and bicarbonate level. Third, determine which abnormalities are primary and which are compensatory based on the pH. If the pH is less than 7.40, then a respiratory or metabolic acidosis is primary. If the pH is greater than 7.40, then a respiratory or metabolic alkalosis is primary. Next, measure the serum electrolytes—sodium, chloride, and total carbon dioxide concentrations—and calculate the anion gap. If the anion gap is 20 mmol per liter or greater, then a metabolic acidosis is present regardless of the pH or serum bicarbonate concentration. If the anion gap is increased, then calculate the excess anion gap (the total anion gap minus the normal anion gap [12 mmol per liter]) and add this value to the measured bicarbonate. If the sum is greater than a normal serum bicarbonate (>30 mmol per liter), then an underlying metabolic alkalosis is present. If the sum is less than a normal bicarbonate (<23 mmol per liter), then an underlying non-

anion gap acidosis is present. Last, determine the cause of each primary disorder that has been identified and begin cause-specific therapy. This approach will allow even complex acid-base disorders to be recognized and will provide a clinically relevant framework for understanding acid-base homeostasis.

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Autocrine Growth Factors and Solid Tumor Malignancy

Moderator
JOHN H. WALSH, MD

Discussants
WILLIAM E. KARNES, MD; FRANK CUTTITTA, PhD; *and* AMEAE WALKER, PhD

This is an edited summary of an Interdepartmental Conference arranged by the Department of Medicine of the University of California, Los Angeles, School of Medicine. The Director of Conferences is William M. Pardridge, MD, Professor of Medicine.

The ability of malignant cells to escape the constraints that normally regulate cell growth and differentiation has been a primary focus of attention for investigators of cancer cell biology. An outcome of this attention has been the discovery that the protein products of oncogenes play a role in the activation of growth signal pathways. A second outcome, possibly related to abnormal oncogene expression, has been the discovery that malignant cells frequently show an ability to regulate their own growth by the release of autocrine growth modulatory substances. Most important, the growth of certain malignant cell types has been shown to depend on autocrine growth circuits. A malignant tumor whose continued growth depends on the release of an autocrine growth factor may be vulnerable to treatment with specific receptor antagonists or immunoneutralizing antibodies designed to break the autocrine circuit. Information is rapidly emerging concerning autocrine growth factors in selected human solid tissue malignancy.

(Walsh JH, Karnes WE, Cuttitta F, Walker A: Autocrine growth factors and solid tumor malignancy. West J Med 1991 Aug; 155:152-163)

JOHN H. WALSH, MD*: Communication between cells is accomplished by the release of "messenger" substances that are delivered to remote target cells through the circulation (endocrine) or to neighboring cells through diffusion (paracrine). When the secreting cell is also the target cell, the term "autocrine" is used (Figure 1). An autocrine substance that stimulates proliferation might cause clonal expansion and tumor formation if negative proliferative influences are not operative or if the cell's life span becomes prolonged. In fact, autocrine-stimulated proliferation has been shown to be a common characteristic of malignant cells in culture. This finding has stimulated tremendous interest in the role of autocrine growth factors in the development and maintenance of malignancy.[1]

Background

WILLIAM E. KARNES, MD†: Malignant cells in culture show several features consistent with autocrine- or paracrine-mediated proliferation: they proliferate in serum-free media containing few (if any) exogenous growth factors,[2] they often secrete growth-promoting peptides, and their growth is enhanced by high plating density.[3] The proof of autocrine-mediated proliferation requires a demonstration that the clones of cells coexpress the putative autocrine growth factor and its specific receptor. In addition, the cells should proliferate in the absence of the exogenous addition of the putative autocrine growth factor and show inhibition of proliferation in the presence of a specific growth factor-receptor antagonist or an immunoneutralizing antibody against the growth factor. Table 1,[4-29] prepared by Frank Cuttitta, MD (author of the Small-cell Lung Cancer section), lists several human malignant tumors, each accompanied by a list of growth factors that have been suggested to be autocrine growth factors.

Can Growth Factors Initiate Malignancy?

Considerable effort has been directed toward determining if autocrine-mediated proliferation is sufficient to promote

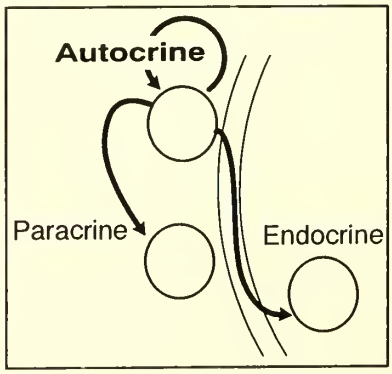

Figure 1.—Communication between cells by soluble factors may occur through the circulation to remote target cells (endocrine) or by diffusion to nearby cells (paracrine). When the secreting cell is the target cell, the term "autocrine" is used.

*Department of Medicine, Division of Gastroenterology/CURE, Wadsworth VA, Los Angeles, California.

†Department of Medicine, Division of Gastroenterology/CURE, Wadsworth VA, Los Angeles, California.

Reprint requests to John H. Walsh, MD, CURE/Wadsworth Department of Veterans Affairs, Bldg 115, Rm 115, Wilshire and Sawtelle Blvds, Los Angeles, CA 90073.

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ABBREVIATIONS USED IN TEXT

EGF = epidermal growth factor
GRP = gastrin-releasing peptide
IGF = insulinlike growth factor
PDGF = platelet-derived growth factor
TGF = transforming growth factor

and maintain malignancy. In the presence of transforming growth factors (TGF-α and TGF-β), normal rat kidney cells become anchorage independent (transformed), a characteristic of malignant cells.[30] When these cells are imparted with an autocrine growth circuit by transfection with an "activated" gene encoding TGF-α (constitutively activated by a promoter sequence), they become transformed in the presence of exogenous TGF-β alone.[31] Similarly, when NIH 3T3 fibroblasts are imparted with a platelet-derived growth factor (PDGF) autocrine circuit by transfection with an activated PDGF gene, a transformed phenotype is produced.[32] Using similar techniques, epidermal growth factor (EGF)-receptor overexpression has also been shown to induce transformation in NIH 3T3 cells in the presence of EGF.[33,34] Finally, and perhaps most significant, the activated expression of TGF-α in transgenic mice has been shown by independent laboratories to induce malignant changes in breast and hepatic epithelium.[35-37] Together these data suggest that autocrine growth circuits may be sufficient to induce and maintain malignancy.

Autocrine-mediated proliferation, however, is not limited to malignant cells. The proliferation of nontumorigenic cell lines derived from normal breast epithelium[38] and a cell line derived from a colonic adenoma[39] has been shown to depend on intact TGF-α- or EGF-receptor autocrine loops. In addition, TGF-α and its receptor are ubiquitous products of many normal tissues, including skin keratinocytes,[40] macrophages,[41] and epithelium of the entire gastrointestinal tract.[42,43] Autocrine-mediated proliferation, therefore, may be a normal phenomenon important in growth, development, and wound repair. Malignancy, however, may be an outcome of the autocrine secretion of growth factors by cells that lack (or lose) the ability to govern the growth signal pathway.

Growth Factors, Oncogenes, Tumor Suppressor Genes, and the Growth Signal Pathway

Progress in the understanding of the role of autocrine growth factors in malignancy has paralleled an explosion of knowledge concerning the genes associated with malignancy: oncogenes and tumor suppressor genes. This progress has led to new insights into the process of malignant transformation. Malignant transformation occurs in response to various defects affecting the growth signal pathway, whether occurring at the level of growth factor-receptor interaction, second messenger systems, or at the level of the nucleus (Figure 2).

Oncogenes are dominantly acting genes that can induce transformation of normal cells into malignant phenotypes (see reviews by Klein, Weinberg, and Bishop[44-46]). They are mutant forms of normal genes that encode protein constituents of the growth signal pathway (Figure 2). For example, growth factors are represented by v-*sis*, which encodes a PDGF-like peptide; v-*erb-b*, which encodes a truncated EGF receptor-like molecule with tyrosine kinase activity (a particularly common characteristic of oncogenes and normal growth factor receptors); the *ras* family of genes encoding guanosine triphosphate-binding proteins, which may be involved in second messenger systems; and, finally, a large group of nuclear oncogenes *(myc, fos, jun)* that encode proteins which seem to regulate the expression of genes important in differentiating and initiating DNA synthesis and cell division. For the most part, oncogene products are constitutively activated forms of their normal counterparts and likely act by causing a short circuit of the growth signal pathway.

Tumor suppressor genes are also associated with malignancy. In contrast to oncogenes, tumor suppressor genes are recessively acting genes; the loss or destructive mutation of both alleles is associated with the development of malignancy (see reviews by Klein and Hansen and Cavenee.[44,47]). Examples of tumor suppressor genes include the RB gene, the loss of which is associated with retinoblastoma,[47] and the p53 gene, the loss of which is associated with colorectal carcinomas.[48] The protein products of tumor suppressor genes seem to play an important role in normal cells to prevent malig-

TABLE 1.—*Possible Autocrine or Paracrine Growth Factors of Human Malignant Tumors*

Peptide	*Tumor*	*Study*
Gastrin-releasing peptide	Small-cell lung cancer	Cuttitta et al, 1985[4]
Insulinlike growth factor I	Fibrosarcoma	DeLarco and Todaro, 1978[5]
	Osteosarcoma	Blatt et al, 1984[6]
	Colon carcinoma	Tricoli et al, 1986[7]; Culouscou et al, 1987[8]
	Liposarcoma	Tricoli et al, 1986[7]
	Breast carcinoma	Furlanetto and DiCarlo, 1984[9]; Huff et al, 1986[10]
	Non-small-cell lung cancer	Minuto et al, 1988[11]; Minuto et al, 1986[12]
	Small-cell lung cancer	Nakanishi et al, 1988[13]
Insulinlike growth factor II	Neuroblastoma	El-Badry et al, 1988[14]
	Leiomyosarcoma	Daughaday et al, 1988[15]
Interleukin-1	Monocytic leukemia	Furukawa et al, 1987[16]
	Acute myelocytic leukemia	Cozzolino et al, 1989[17]
Interleukin-2	T-cell lymphoma	Duprez et al, 1985[18]
Interleukin-6 and B-cell stimulating factor-2	Multiple myeloma	Kawano et al, 1988[19]
Platelet-derived growth factor	Glioblastoma	Hermansson et al, 1988[20]
Transferrin and transferrinlike proteins	Small-cell lung cancer	Nakanishi et al, 1988[21]; Vostres et al, 1988[22]
Transforming growth factor-α	Breast carcinoma	Dickson et al, 1986[23]; Dickson et al, 1986[24]
	Colon carcinoma	Coffey et al, 1986[25]
	Pancreatic carcinoma	Smith et al, 1987[26]
	Non-small-cell lung cancer	Siegfried, 1987[27]
Transforming growth factor-β	Colon cancer	Coffey et al, 1987[28]
	Breast cancer	Knabbe et al, 1987[29]

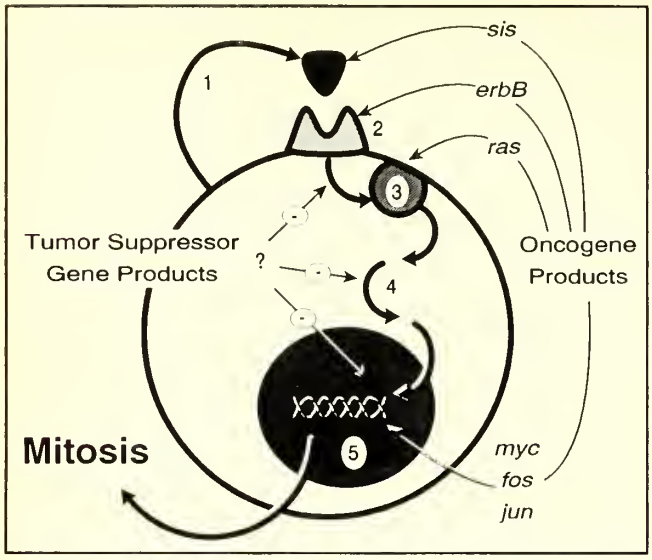

Figure 2.—The relation is shown between representative oncogene products and various steps of the growth signal pathway. Growth factors ① interact with cell surface receptors, ② leading to the activation of second messengers ③ that relay information through the cytoplasm ④ into the nucleus ⑤. Oncogene products are represented at all levels of the growth signal pathway (see text for more detail). Tumor suppressor genes may play an important regulatory role.

nancy, perhaps by tightly regulating key elements of the growth signal pathway.

Autocrine Growth Loops May Be Targets for Therapeutic Intervention

Regardless of the relative roles of oncogenes, tumor suppressor genes, and autocrine growth loops in the process of malignant transformation, autocrine-stimulated proliferation is a common characteristic of malignant cells and is potentially vulnerable to pharmacologic intervention. A malignant tumor whose continued proliferation depends on an intact autocrine growth loop may be vulnerable to treatment strategies that use specific receptor antagonists or growth factor antibodies. This approach has led to phase I clinical trials using monoclonal antibodies to gastrin-releasing peptide (GRP) in patients with advanced small-cell lung cancer.[49]

Autocrine Growth Factors Regulating Proliferation of Pulmonary Malignancy

FRANK CUTTITTA, PhD*: The primary research of our laboratory has focused on identifying and characterizing the autocrine growth factors of human malignant tumors, with an emphasis on small-cell and non-small-cell lung cancers. By understanding tumor cell biology and the factors that regulate growth, we can devise rational therapeutic strategies against malignant disease. We have used three approaches to study the autocrine growth factors of lung cancers:

- *Exogenous requirements for growth factors*

Biologically defined factors are introduced to established cancer cell lines, and their growth-regulating effects (stimulation or suppression) are examined. The responding tumor cells then are analyzed for their ability to produce these biologically active mediators. An example is our studies with insulinlike growth factors (IGFs) and with transferrin, as described subsequently.

- *Endogenous production of growth factors*

When a tumor cell line has shown an abnormal production of a specific peptide hormone, its growth regulatory properties on that same tumor cell line are examined. The growth-promoting properties of gastrin-releasing peptide on human small-cell lung cancer were identified in this manner.

- *Molecular genetic approach to identify new factors*

Genes that encode the transcription of defined growth factors also contain sequence codons for additional peptide products with possible biologic functions. We have identified at least three new peptide products that have growth-promoting effects for normal and malignant cells.[50] These novel factors are encoded within pro-GRP and pro-IGF-I transcripts downstream from the genes' major known peptide products.[51,52]

Gastrin-Releasing Peptide (Mammalian Bombesin) as an Autocrine Growth Factor in Human Small-cell Lung Cancers

Small-cell lung cancer is a highly metastatic neuroendocrine tumor that produces various peptide hormones which can lead to various paraneoplastic syndromes associated with this disease.[53] Under cell culture conditions, small-cell lung cancer cell lines produce arginine vasopressin, adrenocorticotropin, calcitonin, parathyroid hormone-like peptides, luteinizing hormone, human chorionic gonadotropin, IGF-I, oxytocin, neurophysin, estradiol, somatostatin, glucagon, prolactin, endorphin, physalaemin, substance P, and GRP.[54,55] Gastrin-releasing peptide, the mammalian counterpart to the amphibian peptide bombesin, is the first peptide hormone that has been definitively proved to be an autocrine growth regulator of human cancer.[4,56]

Gastrin-releasing peptide has been shown to be an autocrine regulator of human small-cell lung cancer by a series of experimental studies (Table 2).[4,54,57-66] A major factor in the success of these studies was the development of a monoclonal antibody, 2A11, that reacted with the biologically active carboxyl-terminal heptapeptide region of bombesin and GRP.[4] The antibody was exquisitely selective in its binding recognition site and reacted only with biologically active amidated peptide. Antibody 2A11 blocked growth stimulation produced by exogenous GRP in tissue culture and neutralized the biologically active GRP produced by cultured small-cell lung cancer cells. The antibody also caused transplanted small-cell lung cancer tumors in nude mice to shrink, whereas another mouse immunoglobulin G1 antibody raised against an indifferent antigen, MOPC-21, had no effect.

Gastrin-releasing peptide gene expression in fetal and adult lung is confined to a distinct type of pulmonary endocrine cell known as the Kulchitsky cell. This cell is located in the base of normal bronchial epithelium interdigitated between columnar cells.[67,68] Clusters of such cells, known as neuroepithelial bodies, are arranged as apical outcroppings in the bronchial lumen and have been proposed as the progenitor cells for small-cell lung cancer.[69,70]

The increased production of GRP in small-cell lung cancer tumors and cell lines was confirmed in several laboratories.[54,57-59] Subsequently the complementary DNA encoding prepro-GRP was isolated from small-cell lung cancer lines.[71] The gene has been mapped to human chromosome 18q21.[72] The messenger RNA for GRP is subjected to

*Department of Medicine, Uniformed Services, University of the Health Sciences, and NCI-Navy Medical Oncology Branch, National Naval Medical Center, Bethesda, Maryland.

TABLE 2.—*Studies of the Role of Gastrin-Releasing Peptide (GRP) in Human Small-cell Lung Cancer*

Results	*Study*
GRP was shown to be an endogenous product of small-cell lung cancer	Moody et al, 1981[54]; Wood et al, 1981[57]; Yamaguchi et al, 1983[58]; Erisman et al, 1982[59]
GRP was found to be actively secreted by small-cell lung cancer	Moody et al, 1983[60]; Korman et al, 1986[61]; Sorenson et al, 1982[62]
Small-cell lung cancer was found to express high affinity receptors of GRP	Moody et al, 1983[63]; Moody et al, 1985[64]
Exogenously administered GRP stimulated clonigenic growth of cultured small-cell lung cancer	Carney et al, 1987[65]
Endogenously produced GRP was shown to induce autoproliferation of small-cell lung cancer	Cuttitta et al, 1985[4]
A monoclonal antibody that immunoneutralizes the growth-promoting effects of exogenous GRP and bombesin on small-cell lung cancer neutralized the growth factors released into culture medium by the same cell lines	Cuttitta et al, 1985[4]
The same monoclonal antibody blocked growth of tumors of small-cell lung cancer transplanted into nude mice	Cuttitta et al, 1985[4]
Competitive antagonist peptides that interact with the GRP receptor but produce no biologic response prevented interaction of GRP with its receptor and inhibited small-lung cancer growth in vitro	Trepel et al, 1988[66]

alternative splicing, resulting in the formation of three different mRNA products.[71] All three mRNAs code for precursor molecules with a common GRP region but differ as to their downstream amino acid composition on the carboxyl-terminal side. One alternatively spliced precursor product (pro-GRP II) differs from the largest gene product (pro-GRP I) by a 7-amino acid truncation due to a 21-base deletion in its mRNA. The shortest GRP message has a 19-base deletion, which in turn leads to a frame shift in amino acid coding that results in the formation of an entirely new peptide at the carboxyl terminus (pro-GRP III). Polyclonal antibodies have been raised against both of these carboxyl-terminal amino acid sequences and used to characterize prepro-GRP expression in normal and malignant lung tissues.[73] Immunohistochemical studies have shown that both peptide I or II and peptide III gene products are produced by normal and malignant pulmonary endocrine cells.[73]

Peptides that result from the alternate splicing of GRP mRNA have been isolated and characterized from small-cell lung cancer cell lines.[52] One of these was the C-terminal tetradecapeptide of prepro-GRP III. A synthetic analogue of this peptide was shown to bind with high affinity (2 nmol per liter) to specific receptors on small-cell lung cancer cells that did not interact with GRP. There is some preliminary evidence that this peptide may be another growth-stimulating product of the GRP gene for small-cell lung cancer.

A 78-kd protein has been putatively identified as the GRP receptor in small-cell lung cancer.[64] Small-cell lung cancer cells have a relatively low number of receptors on their surface, on the order of 1,000 to 3,000 per cell, with a ligand binding constant of approximately 1 nmol per liter. Neither the tumor receptor nor the normal receptor has yet been cloned and sequenced.

The growth-stimulating properties of GRP on small-cell lung cancer usually show a narrow concentration range for the optimal stimulation of clonigenic growth with an inhibition of growth by supramaximal doses.[65] Optimal concentrations of GRP for stimulating the growth of small-cell lung cancer cells usually are 10 to 100 nmol per liter. Gastrin-releasing peptide has also been shown to stimulate the growth of normal bronchial epithelial cells in culture.[74]

Insulinlike Growth Factor I in Small-cell Lung Cancer

Insulin is known to be a factor that enhances the growth of small-cell lung cancer and many other human tumor cell lines.[75] In humans, insulinlike growth factors (IGF-I and IGF-II) are products of separate genes and interact with high-affinity receptors distinct from the high-affinity insulin receptor.[76-83] Insulinlike growth factors I and II are known to play an important role in regulating mammalian growth during fetal development.[84] Several studies with primary human non-small-cell lung cancers showed increased levels of IGF-I.[11,12]

We studied the effects of insulin on small-cell lung cancer and found that the proliferation of growth it induced was not mediated through the high-affinity insulin receptor.[13] Using reagents that had been applied to study the regulation of growth of 3T3 cells,[85,86] we found that a monoclonal antibody to the IGF-I receptor, α-IR-3, neutralized the insulin-induced growth of small-cell lung cancer without binding to the insulin receptor. Recombinant IGF-I was shown to be more potent than insulin in stimulating the growth of small-cell lung cancer in vitro, and this stimulation was blocked by monoclonal antibody α-IR-3,[13] providing additional evidence that the IGF-I receptor was dominant in stimulating the growth of small-cell lung cancer by both insulin and IGF-I.

To establish whether or not IGF-I had an autocrine stimulatory role in small-cell lung cancer, we developed antibodies against IGF-I and IGF-I gene-related peptides predicted from cDNA analysis of IGF-I to be located downstream (carboxyl-terminal) to IGF-I in prepro-IGF-I. These polyclonal antibodies were used to screen whole cell lysates of several small-cell lung cancer lines for the expression of IGF-I and IGF-I gene-related peptides. Several cell lines were found to produce these peptides. Endogenously secreted IGF-I was found to retain full biologic activity to initiate the growth of other small-cell lung cancer cell lines, and monoclonal antibody α-IR-3 lowered the growth rate of small-cell lung cancer cell lines.[13] These data imply that IGF-I produced by some small-cell lung cancer cell lines functions as an autocrine regulator of tumor cell growth.

Transferrin in Small-cell Lung Cancer

We have identified transferrin or transferrinlike protein as an additional autocrine growth factor in small-cell lung cancer.[21] This finding has been confirmed by another laboratory.[22] Our studies on transferrin were similar to studies we did with IGF-I. The initial experiments showed that small-cell lung cancer cell lines used transferrin to maintain growth. In serum-free culture conditions, transferrin is used

as the iron-binding protein to satisfy cellular cofactor demands of the electron transport system. Several small-cell lung cancer cell lines can grow in the absence of exogenous transferrin. Because there are no known biologic substitutes for transferrin, such a finding implicated the endogenous production of transferrin or a transferrinlike protein. On further investigation, it was found that the growth of small-cell lung cancer cell lines could be blocked by the use of a monoclonal antibody to the transferrin receptor, MoAb 42/6.[21,87,88] Subsequent studies have shown that small-cell lung cancer cell lines produce an 80-kd protein that shares immunologic homology with native transferrin.[22] All these data show that transferrin or other transferrinlike proteins, or both, initiate the autocrine growth of small-cell lung cancer in vitro.

Conclusions

We have shown that GRP, IGF-I, and transferrin can function as autocrine regulators of the growth of small-cell lung cancer cell lines in vitro. The autocrine growth-promoting role of GRP has also been shown in vivo. These studies have expanded our understanding of the growth regulation of small-cell lung cancer and have brought us closer to the development of new therapeutic strategies based on the interruption of autocrine growth stimulants. Current strategy has involved the use of neutralizing antibodies raised against tumor growth factors or their respective receptors to block autocrine loop mechanisms of proliferation. Future directions will include the development of specific growth factor receptor chemical antagonists and cytotoxic reagents that are targeted to growth factor receptors.

Breast Carcinoma

AMEAE M. WALKER, PhD*: The pivotal role of estrogens as promoters of human breast cancer is well established. The estrogen dependency of many breast cancers has permitted effective treatments using antiestrogens or oophorectomy. Unfortunately, by the time breast cancer reaches the stage of overt metastatic disease, estrogen dependence is frequently lost.[89] The search for an understanding of the estrogen promotion process and the mechanisms whereby most of the tumors subsequently escape estrogen dependence has led to evidence that estrogen may stimulate the proliferation of breast cancer cells by modulating the release of, and response to, autocrine and paracrine growth factors.[90]

Several autocrine growth factors have been shown to be elaborated by breast cancer cells in culture and in some cases by normal breast tissues in vitro and in vivo (Table 3). The secretion of many of these factors has been shown to be regulated by estrogen. The growth-promoting peptides, TGF-α, IGF-I, and 52K-cathepsin D, are positively regulated by estrogen, whereas the growth-inhibiting peptide, TGF-β, is negatively regulated by estrogen. Other potential autocrine growth-regulating peptides now being studied in breast cancers include IGF-II, basic fibroblast growth factor, platelet-derived growth factor, and the recently recognized growth-inhibiting peptide, mammostatin.[91]

Transforming Growth Factor-α

Of the growth-stimulating factors, TGF-α, which has received the most attention, is a 5.6-kd, 50-amino acid polypeptide that is structurally similar to EGF and probably acts

TABLE 3.—*Estrogen-Responsive Growth Factors in Human Breast Carcinoma*

Peptide	*Route*	*Growth*	*Estrogen Effect on Release*
Transforming growth factors-α	Autocrine	↑	↑
Insulinlike growth factors I	Autocrine	↑	↑
52K-Cathepsin D	Autocrine	↑	↑
Insulinlike growth factor II	(Autocrine?)	↑	↑
Basic fibroblast growth factor	(Autocrine?)	↑	?
Platelet-derived growth factor	(Paracrine?)	↑(Stroma)	?
Transforming growth factors-β	Autocrine	↓	↓
Mammostatin	(Autocrine?)	↓	?

through the EGF receptor. In 1984 Salomon and colleagues showed that conditioned medium from mammary tumor cells competed with EGF labeled with iodine 125 for EGF receptor binding on 3T3 fibroblasts and stimulated the growth of normal rat kidney cells in soft agar.[92] These workers also found EGF receptors on the same mammary tumor cells that released EGF-receptor binding activity. This work has been verified and extended by Dickson and associates,[23,93] who found that EGF-receptor binding activity was TGF-α. The ability of these cells to produce TGF-α and growth response to exogenous TGF-α suggests an autocrine role in mammary carcinoma. The fact that approximately 70% of primary mammary tumors express TGF-α mRNA[94] and as many as 67% possess EGF receptor[95] emphasizes the possible importance of this autocrine circuit in breast cancer.

The expression and secretion of TGF-α seem to be tightly regulated by estrogen in estrogen-sensitive cells. Several mammary tumor cell lines have been shown to produce anywhere from two to eight times more TGF-α in response to estrogen administration, whereas estrogen depletion or treatment with antiestrogens leads to much lower production,[23,94] an effect that is paralleled by the stimulation and inhibition of growth, respectively.[96] Epidermal growth factor-receptor expression also seems to be positively regulated by estrogen[97,98] and EGF.[99] The growth-inhibiting effect of antiestrogens on breast cancer cell lines can be reversed by the exogenous administration of EGF.[100] Taken together, these observations suggest that TGF-α autocrine secretion is mediated by estrogen in estrogen-dependent cell lines.

Bates and co-workers tested the dependency of estrogen-stimulated growth on the autocrine secretion of TGF-α in estrogen-sensitive cells (MCF-7).[94] Immunoneutralizing anti–TGF-α antibody and EGF-receptor antagonist antibodies each significantly inhibited estrogen-induced growth after several days. These results contrast with those of Arteaga and colleagues, who were unable to show an inhibition of estrogen-induced DNA synthesis by anti–TGF-α antibody or EGF-receptor antagonist after 18 hours using MCF-7 cells.[101] In the latter study, cells were pretreated with tamoxifen to accentuate the estrogen response. A role of TGF-α as the mediator of estrogen-induced growth of breast carcinoma was further disputed by the work of Clarke and associates.[102] They transfected MCF-7 cells with an activated TGF-α gene to induce constitutive overexpression and secretion of TGF-α. Although the transfected cell lines secreted large amounts of TGF-α, they remained estrogen-dependent and were unable to form tumors in oophorectomized nude mice. In summary, much evidence suggests an important role for TGF-α in stimulating the growth of estrogen-responsive breast carci-

*Department of Biomedical Sciences, University of California, Riverside.

noma cells, although the role of TGF-α as a mediator of estrogen-induced growth is disputed.

Insulinlike Growth Factor I

Insulinlike growth factor I is a 7.6-kd polypeptide with considerable structural similarity to proinsulin. Although IGF-I is able to bind insulin receptor and stimulate many of insulin's metabolic effects, it exerts its mitogenic effect through interaction with its own specific receptor. Insulinlike growth factor I is a potent mitogen for breast cancer cells in vitro.[103] Like TGF-α, IGF-I can override the growth-inhibitory effects of tamoxifen.[96] Insulinlike growth factor-I receptors are present on most of breast carcinoma cell lines[104,105] and primary breast carcinomas,[106] whereas few, if any, IGF-I receptors are detectable in normal breast tissues.[107,108] The receptor content of IGF-I is positively correlated with estrogen receptor content in primary tumors.[106,108] Like TGF-α, IGF-I release seems to be stimulated by estrogen,[109] although estrogen may not be the primary regulator.[103]

52K-Cathepsin D

52K-Cathepsin D, a glycoprotein precursor of the 34-kd protease, cathepsin D,[110,111] is secreted by and is mitogenic for breast carcinoma cell lines. Its secretion is induced by estrogen in estrogen-dependent cell lines,[112] and it is mitogenic for the same cells in the absence of estrogen.[113] Its expression is also induced by EGF, insulin, IGF-I, and basic fibroblast growth factor.[114] In estrogen-independent cell lines, 52K-cathepsin D is constitutively expressed.[115] The mechanism by which it stimulates proliferation is unclear. It may function enzymatically to activate or inactivate co-secreted growth-promoting or -inhibiting propeptides, respectively.[116,117] Alternatively, it may exert its mitogenic effects directly. Morgan and colleagues found a high degree of structural similarity between the mannose-6-phosphate receptor and the IGF-II receptor.[118] Because cathepsin D bears mannose-6-phosphate moieties and binds mannose-6-phosphate receptors,[119] it may have the capacity to interact with IGF-II receptor to induce mitogenesis directly. Finally, cathepsin D may function to enhance tumor invasiveness by its proteolytic activities on basement membrane components.[120]

Insulinlike Growth Factor II

Insulinlike growth factor II is structurally related to IGF-I and proinsulin and binds a unique receptor.[121] Yee and associates showed that IGF-II is produced by and is mitogenic for breast cancer cells in vitro.[122] They also found that IGF-II production, like most of the other growth factors mentioned above, is induced by estrogen in estrogen-sensitive cell lines. Specific receptors and several binding proteins for IGF-II have been found in most breast carcinoma cell lines.[105] Insulinlike growth factor II mRNA is frequently expressed and produced by human mammary carcinomas and by surrounding normal tissues,[122] suggesting that this peptide may prove to be an important autocrine or paracrine growth regulator of breast carcinoma.

Fibroblast Growth Factors and Platelet-derived Growth Factor

Fibroblast growth factor-related genes have been shown to be amplified and expressed in approximately 17% of primary breast carcinomas.[123,124] Basic fibroblast growth factor stimulates the proliferation of breast carcinoma cells in vitro.[103,125] Platelet-derived growth factor-related proteins are also produced by breast cancer cells and surrounding stromal tissue but do not stimulate autogrowth of breast cancer cells.[126-128] They may contribute to tumor growth by stimulating stromal proliferation.

Transforming Growth Factor-β—A Growth Inhibitor

The fourth growth factor listed in Table 3, TGF-β, has received much attention because of its ability to inhibit the growth of many epithelial carcinomas. Transforming growth factor-β represents a family of structurally related peptides that bind to specific receptors.[129,130] In the presence of EGF, TGF-β will induce colony formation of normal rodent fibroblast cells in soft agar.[30] This growth factor is particularly interesting because, contrary to its growth-stimulating effects on normal rat kidney cells in soft agar, it has a growth-inhibiting effect on normal rat kidney cells when grown in monolayers. It is capable of stimulating or inhibiting a wide variety of cell types.[131] Growth inhibition by TGF-β is most often seen in cells of epithelial origin, including mammary tumor cells.[29]

Mammary tumor cells frequently produce TGF-β, bear receptors for TGF-β, and increase their production of TGF-β in response to antiestrogens or estrogen withdrawal.[29] In estrogen-responsive cell lines, estrogen causes a reduction in TGF-β production,[23] whereas antiestrogens or estrogen withdrawal induces TGF-β production.[29] The inhibitory effects of estrogen on the production of TGF-β and its stimulatory effects on the production of growth-promoting peptides can easily be envisioned as a mechanism explaining the estrogen dependence of mammary tumors. Other estrogen-dependent mammary carcinoma cell lines do not follow this pattern, however, as judged by the effects of estrogen on mRNA levels of TGF-α and TGF-β.[132] There are probably other mechanisms of estrogen promotion.

Escape From Estrogen Dependence

We can well envision an escape from estrogen dependence resulting from the constitutive production of autocrine growth factors or the underproduction of autocrine growth-inhibitory factors (TGF-β). In line with this hypothesis is the finding that EGF causes a decrease of estrogen-receptor levels in estrogen-sensitive cell lines.[133] Dickson and coworkers, however, found a complete lack of correlation between estrogen dependence or tumorigenicity and the overproduction of TGF-α, or the underproduction of TGF-β, in breast carcinoma cell lines.[23] In addition, estrogen receptor-positive cell lines frequently lack TGF-β receptor, and their growth is not greatly inhibited by exogenous TGF-β, whereas estrogen-negative cell lines often bear TGF-β receptor, and their growth is potently inhibited by TGF-β.[134] Finally, the TGF-α content of estrogen receptor-negative primary mammary carcinomas has been found to be reduced by 50% compared with estrogen receptor-positive tumors.[135]

Battaglia and associates reported a substantially higher incidence of EGF-receptor positivity in metastatic lesions compared with primary tumors.[136] Using immunocytochemical techniques, the same group and others found a significant inverse relation between staining for EGF receptor and estrogen receptor in primary breast tumors, respectively.[108,136,137] In other studies by Nicholson and colleagues

using immunocytochemical and radioreceptor assay techniques on tumors removed after antiestrogen therapy, a strong positive relation between a poor response to antiestrogen therapy and EGF-receptor positivity or estrogen-receptor negativity was found.[138,139]

*HER-2/*neu *Oncogene Products Are Related to Estrogen Independence and Poor Prognosis*

Recently the amplification of an EGF-receptor–related proto-oncogene variously known as HER-2, *neu*, or c-*erb* B2, has been seen in 25% to 30% of primary breast carcinomas.[140] The HER-2/*neu* proto-oncogene has been shown to be inversely associated with estrogen- and progesterone-receptor status[141] and negatively correlated with prognosis.[140] Presumably it encodes a growth factor receptor, but its ligand has not yet been identified.

Escape from estrogen dependence seems to be better correlated with the expression of the EGF receptor and its closely related family member (HER-2/*neu*) than to the expression of TGF-α or TGF-β. This finding does not exclude the possibility that other as-yet-unidentified growth-modulating ligands may be important in the process of estrogen escape. It does, however, emphasize that a short circuit of the growth signal pathway does not have to be autocrine. Constitutively activated receptors, second messenger systems, or primary growth signals at the level of the nucleus could lead to autonomous growth independent of extracellular modulatory substances. The complex interactions between intracellular and extracellular events in the growth signal pathway remain poorly understood.

Gastrointestinal Cancers

Dr Karnes: Autocrine growth circuits in gastrointestinal cancers have been less well characterized than those of breast cancer and small-cell lung cancer. Data are emerging in support of the importance of autocrine growth factors in gastrointestinal malignant tumors. Growth factors attracting the most attention have included TGF-α, TGF-β, and gastrin. The strongest data to date involve the autocrine role of TGF-α in cancers of the esophagus, stomach, pancreas, and colon.

Transforming Growth Factor-α

Esophagus. Squamous cell carcinoma of the esophagus is associated with the amplification and overexpression of the EGF–receptor gene.[142] Tissue and cell lines derived from squamous cell carcinoma of the esophagus also have an elevated receptor number compared with other carcinomas.[143,144] Yoshida and co-workers recently showed coexpression of the EGF receptor and its ligand, TGF-α, in all six esophageal squamous carcinoma cell lines they tested.[145] Messenger RNA and protein of EGF were also produced in three of the six cell lines. Monoclonal antibodies against EGF and TGF-α inhibited DNA synthesis in one of these cell lines, suggesting that EGF and TGF-α functioned as autocrine growth factors.

Stomach. As in squamous cell carcinoma of the esophagus, gastric carcinoma tumor specimens and cell lines almost universally express EGF receptors.[146-148] Similarly, the EGF-receptor ligands, TGF-α and EGF, are also produced by gastric carcinoma cell lines.[149,150] The level of EGF-like immunoreactivity in gastric carcinoma tissues has been associated with a poor prognosis.[149] An autocrine role of TGF-α and EGF in gastric carcinoma has been suggested by Yoshida and colleagues in work similar to that described in esophageal carcinoma cell lines.[151] They found that TGF-α and EGF receptor were coexpressed in all 7 gastric carcinoma cell lines and in all 15 gastric carcinoma tumors they examined. Furthermore, they showed that antibodies against TGF-α and EGF inhibited DNA synthesis of cultured cell lines.

Pancreas. Two pancreatic carcinoma cell lines have been shown by Smith and associates to possess EGF receptors, express and release TGF-α, and proliferate in response to exogenous EGF or TGF-α (TGF-α was 10 to 100 times more potent than EGF).[26] They further noted that cells that produced TGF-α also overexpressed EGF receptor, suggesting a superagonist autocrine cycle involving TGF-α and EGF receptor. These authors, however, did not extend their study to show that the cells could grow in the absence of exogenous EGF or TGF-α and that growth under these conditions could be specifically inhibited by the addition of neutralizing anti–TGF-α antibody or EGF-receptor antagonist.

Colon. Colon cancer cell lines often show a density-dependent stimulation of cell growth, and conditioned media from these lines can stimulate the growth of other cell lines, implying the production and secretion of growth factors into the conditioned media.[152] In most colon cancer cell lines that have been examined, TGF-α and EGF or TGF-α receptor are coexpressed.[28,152-155] The EGF-receptor antagonist, anti–EGF-receptor monoclonal antibody 425, has been shown by Rodeck and associates to inhibit the growth of a human colon carcinoma cell line in nude mice.[156]

In our laboratory, we have shown that the colon carcinoma cell line, SNU-C1, coexpresses TGF-α and its receptor and releases TGF-α into serum-free conditioned medium.[157] We have further shown that this cell line has the ability to proliferate autonomously in serum-free medium containing no exogenous growth factors and shows a significant proliferative response to exogenously added TGF-α, EGF, or serum-free medium conditioned by SNU-C1 cells. Using an EGF receptor-blocking monoclonal antibody, we have shown that the autonomous proliferation of SNU-C1 cells is entirely dependent on EGF-receptor activation by an autocrine EGF-receptor ligand, most likely TGF-α.[157] Future studies in additional cell lines will be needed to determine if the dependency of proliferation on the autocrine secretion of TGF-α is a common phenomenon in colon carcinomas.

Transforming Growth Factor-β

Almost all published work with TGF-β in gastrointestinal malignancy has been in colon carcinoma. Anzano and co-workers found TGF-β in 16 of 18 colon cancer cell lines.[152] In addition, colon cancer cell lines frequently possess specific high-affinity TGF-β receptors and have a growth-inhibitory response to TGF-β.[158] Interestingly, the growth-inhibitory response to TGF-β was more apparent in well-differentiated cell lines than in those more poorly differentiated. Growth inhibition by TGF-β has been verified by other investigators[159,160] but has not always been found.[25] More work is needed to establish the role of TGF-β as an autocrine growth-inhibitory factor in gastrointestinal cancers.

Gastrin

Recent evidence suggests a role of gastrin as an endocrine or paracrine (autocrine) growth stimulant of colon and gas-

TABLE 4.—*Functions of Elevated Extracellular Prolactin*

Function	*Time*	*Study*
Inhibits further prolactin secretion	Immediate	Kadowacki et al, 1984[173]
Results in the reuptake of already secreted prolactin	Immediate	Kadowacki et al, 1984[173]; Giss and Walker, 1985[174]
Promotes the degradation of newly synthesized prolactin	After 4 h	Kadowacki et al, 1984[173]
Inhibits prolactin synthesis	12 to 24 h	Walker et al, 1988, unpublished data

tric carcinomas. In addition to gastrin's prosecretory effects on the gastric mucosa, it also has been reported to have a trophic effect on normal gastric and colonic mucosa and on human colon carcinoma cell lines in nude mouse xenografts.[161-163] The proliferation of some colon cancer cell lines, particularly those that are well differentiated, is stimulated by exogenous gastrin.[164,165] Several colon and gastric carcinoma cell lines are known to have gastrin receptors,[166-169] and some colon carcinoma cell lines also express gastrin mRNA, suggesting a possible autocrine role of gastrin.[170] The gastrin antagonist, proglumide, and gastrin antibodies inhibit the growth of gastrin-responsive colon cancer cells in culture and in xenografts.[165,170,171] Although a role of circulating gastrin in colon cancer development is suggested by evidence that serum gastrin values are increased in patients with colon cancer,[172] there are few studies of the mechanism of action of gastrin to stimulate colon cancer proliferation.

Autocrine Regulation of Pituitary Tumor Growth and Secretion by Prolactin Isoforms

DR WALKER: For several years we have been interested in the autocrine regulation of prolactin secretion.* This interest has expanded to include the autocrine regulation of pituitary cell differentiation and proliferation. By autocrine regulation of prolactin secretion, we mean the ability of already secreted prolactin to inhibit further prolactin secretion from the same or an equivalent cell in the pituitary. Table 4 lists the results we obtained using primary cultures of rat anterior pituitary cells as a model system.[173,174]

One of the puzzling findings of these studies was that although autocrine regulation led to lysosomal degradation of newly synthesized prolactin,[173] the prolactin taken back up by the cells was never deposited in lysosomes.[174] Because the cell was able to distinguish between these two prolactins, we studied intracellular versus extracellular forms of prolactin. Many prolactin variants have been described.[175] For the purposes of autocrine regulation, only the charge variants of monomer prolactin seem to be important. These have the same molecular weight but vary in their degree of net negative charge. They have been described for all species examined, including humans.[176]

Inside pituitary cells there are three to four of these forms, called isoforms. Isoform 2 is always the predominant form, although the ratios of the forms differ under different physiologic circumstances.[177] The major forms in the medium are isoforms 2, 3, and 3′. In the medium, forms 3 and 3′ regularly appear as greater percentages of the total isoform amount than they do inside the cells. This finding suggested the possibility that 3 or 3′, or both were responsible for autocrine regulation and that form 2 would be the newly synthesized form directed to lysosomes. To test this hypothesis, we investigated the isoforms synthesized and secreted by a rat tumor cell line (GH3 cells[178]) that does not normally autoregulate its prolactin secretion. These cells were found to synthesize and secrete only isoform 2.[179] The tumor cells could, however, be induced to autoregulate by adding prolactin from normal sources that contained isoforms 2, 3, and 3′. The retained ability of these cells to autoregulate was first shown by Melmed and associates.[180] These results clearly suggest that isoform 2 is inactive in autocrine regulation, whereas isoforms 3 or 3′, or both, are important.[179]

In 1986 we showed phosphorylation of prolactin isoforms 3 and 3′ in intact pituitary cells.[181] Recently we have established that only isoform 2 is translated from normal pituitary messenger RNA in an in vitro system containing rough microsomes.[182,183] We might therefore conclude that isoforms 3 and 3′ are formed from isoform 2 by serial phosphorylation. The finding of prolactin kinase activity in secretory granules[182] shows that this phosphorylation does not occur until late in biosynthesis and storage, possibly even just before exocytosis of a prolactin secretory granule (Figure 3).

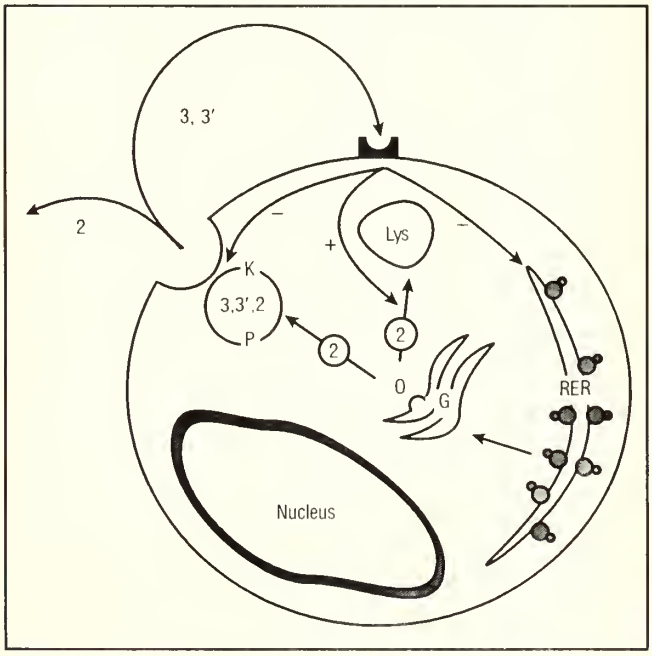

Figure 3.—A schematic representation of prolactin isoform biosynthesis, secretion, and secretory autocrine activities is given. Prolactin is synthesized on the rough endoplasmic reticulum **(RER)** as isoform 2. Isoform 2 moves through the Golgi complex **(G)** where it is packaged into small immature secretory granules. Newly synthesized granules can be diverted for digestion in a lysosome **(Lys)**, should autocrine inhibition of secretion be operative, or they can be permitted to mature until they contain isoform 3 and 3′. Secretion of all 3 isoforms occurs, but for secretory control only isoforms 3 or 3′ or both reinteract with the cell through the autoreceptor. Interaction with the autoreceptor or subsequent internalization of prolactin, or both, inhibit prolactin release, stimulate lysosomal digestion of newly synthesized prolactin, and inhibit prolactin synthesis. Kinase **(K)** phosphorylates prolactin, and phosphatase **(P)** removes phosphate.

*W. F. Young, Jr, MD, E. R. Laws, Jr, MD, and B. Scheithauer, MD, of the Mayo Clinic, Rochester, Minnesota, have collaborated with the author in the study of human prolactinoma tissue.

Having established that the autocrine regulation of prolactin secretion could be induced in the tumor cells by using the correct isoform, we wondered whether this induction resulted in any changes in tumor cell ultrastructure. Normal prolactin-secreting anterior pituitary cells are highly differentiated cells. They contain abundant and regularly arrayed rough endoplasmic reticulum, a large and polarized Golgi apparatus, and an abundance of prolactin storage granules.[184] The GH3 cells and most prolactin-secreting cell lines and tumors, on the other hand, contain sparse and irregular rough endoplasmic reticulum, dispersed Golgi elements, and few (sometimes none) small secretory granules.[185] The initiation of autocrine regulation in the tumor cells resulted in the development of more rough endoplasmic reticulum, an organized and polar Golgi apparatus, and the storage of many more prolactin granules.[186] Because granulation of these cells occurs by co-treatment with estrogen, insulin, and EGF,[187] we tested these hormones for their ability to induce isoforms 3 and 3′. Insulin (as used by Scammel and colleagues[187] at 300 nmol per liter) and IGF-I and IGF-II at 10 and 100 ng per ml, respectively, were each able to induce the production of isoforms 3 and 3′.[188] We tentatively concluded that the induction of a more normal phenotype in the tumor cells, whether initiated by prolactin or growth factors, operates by the autocrine route.

With the induction of a phenotype geared towards secretion, rather than cell division, do prolactin autocrine effects have any influence on cell proliferation? GH3 cells plated at low cell density (that used in many laboratories) respond to exogenous prolactin by proliferating, plated at intermediate density appear unaffected by the addition of prolactin, and plated at high density respond to prolactin by a substantial inhibition of cell proliferation. The biphasic response to exogenous prolactin is difficult to interpret at present. It may be necessary for prolactin to interact with another autocrine growth factor to exert its inhibitory effect on proliferation. A suitable factor would be IGF-I, which we have shown induces the correct isoform and is produced by GH3 cells.[189] It is also possible that isoform 2 stimulates proliferation, isoforms 3 or 3′, or both, inhibit proliferation, and specific receptors for each form are present on the surface of the cells when the cells are cultured at different densities. Consistent with the hypothesis that isoform 2 is autoproliferative and isoform 3 is antiproliferative are the results of recent in vivo studies of isoform profile changes during diethylstilbestrol induction of prolactinomas.[190] Initial analysis of human macroprolactinoma tissue also shows the absence of isoforms 3 and 3′ (Walker and co-workers, unpublished results, 1988). It is possible therefore that our results using rat model systems are directly applicable to the human condition.

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Hepatitis C Virus
A Review

EDDIE TANG, MD, *Los Angeles, California*

This paper was chosen as the winner of THE WESTERN JOURNAL OF MEDICINE's 1991 Medical Student Writing Competition. The contest was open to all students attending medical schools in the West and will be repeated annually.

LINDA HAWES CLEVER, MD
Editor

Hepatitis C virus has been shown to be responsible for most cases of posttransfusion hepatitis, as well as for sporadic non-A, non-B viral hepatitis. Hepatitis C virus has also been implicated in the development of primary hepatocellular carcinoma, autoimmune hepatitis, and fulminant viral hepatitis. Although the role of the parenteral transmission of hepatitis C virus is well established, its route of transmission in cases of sporadic infection remains unclear. Sexual transmission is suspected but not confirmed. Recent work regarding treatment has shown interferon alfa to be effective, but the discontinuation of therapy is associated with a 50% relapse rate.

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Hepatitis develops in nearly 10% of all blood transfusion recipients.[1] In the United States alone, this translates into more than 15,000 new cases each year of cirrhosis caused by transfusion.[2] In the early 1970s, posttransfusion hepatitis was thought to be due to the hepatitis B virus (HBV). With the development of sensitive assays for hepatitis B surface antigen (HBsAg), it became clear that HBV was responsible for less than 25% of such cases.[1] Serologic tests for hepatitis A virus (HAV) likewise showed HAV to be rarely responsible. The term non-A, non-B hepatitis was, therefore, adopted for these cases. With the introduction of routine screening of blood donors for serum HBsAg, 90% to 95% of cases of posttransfusion hepatitis have become characterized as non-A, non-B hepatitis.[1]

Numerous attempts have been made to find the cause of non-A, non-B hepatitis. Until recently, however, the responsible agent had remained elusive, and no screening tests were available. As a result, surrogate markers associated with an increased risk for non-A, non-B hepatitis transmission were identified and used to screen blood donations. The markers found to be useful were elevations of serum alanine aminotransferase levels and the presence of anti-hepatitis B core antibody (HBcAb).

Breakthrough

In 1988, workers at Chiron Corporation announced the discovery of viral antigens specific for posttransfusion non-A, non-B hepatitis.[3] They isolated all nucleic acid from known infectious serum and, from this pool, formed complementary DNA fragments using reverse transcriptase with random primers. This process yielded approximately 6 million sequences complementary to random segments of nucleic acid found in the infectious serum. These sequences were then individually inserted into phage vectors and expressed in *Escherichia coli*. Each resulting polypeptide was tested with serum from patients with chronic non-A, non-B hepatitis to detect reactivity with serum antibodies. Each polypeptide was also screened with control specimens of noninfected serum. After about a million such specimens were screened, one was found to react with antibodies in infected serum but not with control serum.

The complementary DNA fragment used to generate this polypeptide was then used as a hybridization probe to extract the original nucleic acid from which the fragment was generated. In this way, the entire genome of the suspected agent was identified. It was found to be composed of a single positively stranded RNA about 10,000 nucleotides long. From homologies found within the genomic structure, it appeared that this agent, now termed hepatitis C virus (HCV), was related to the family of togaviruses or flaviviruses. This identification was consistent with the 30- to 60-nm size of the virus,[4] as determined by filtration studies, and with the presence of a viral envelope, as recognized by the agent's sensitivity to chloroform.[5]

To develop a serologic test for HCV, a segment of DNA based on the one that produced the original reactive polypeptide was inserted into a plasmid. This viral segment, coding for 363 amino acids from the nonstructural portion of the viral genome, was first ligated with the gene for superoxide dismutase before insertion in order to increase polypeptide production. The resulting protein sequence was expressed in yeast culture and used as the antigen basis for radioimmunoassay and enzyme-linked immunosorbent assay (ELISA).

Epidemiology

To assess the role of the newly identified HCV as the etiologic agent for posttransfusion non-A, non-B hepatitis, Van Der Poel and colleagues in 1989 studied nine cardiac surgery patients with documented posttransfusion non-A, non-B hepatitis and nine matched controls.[5] Serial serum specimens from patients having cardiac surgery showed that four seroconverted, as compared with none of the nine con-

From the University of Southern California School of Medicine, Los Angeles.
Reprint requests to Eddie Tang, MD, 2141 Alta St, #10, Los Angeles, CA 90031.

ABBREVIATIONS USED IN TEXT

ALT = alanine aminotransferase
CID = chimp infectious dose
ELISA = enzyme-linked immunosorbent assay
HAV = hepatitis A virus
HBcAb = hepatitis B core antibody
HBsAg = hepatitis B surface antigen
HBV = hepatitis B virus
HCV = hepatitis C virus
HIV = human immunodeficiency virus

trols. Furthermore, seven of the nine surgical patients had donor serum that was HCV-positive. In a prospective study of 34 patients with posttransfusion non-A, non-B hepatitis in Spain, 4 (12%) became seropositive by 8 weeks, 15 (44%) by 28 weeks, and 27 (79%) by 52 weeks.[6] Other studies also have found the prevalence of HCV-positivity in cases of posttransfusion non-A, non-B hepatitis to be about 80%.[7,8]

Various factors appear to affect the rate of HCV seroconversion. First, a long time lag before seroconversion is observed using the currently available tests. Studies in the United States have shown conversion rates of 32%, 71%, and 81% in patients with acute disease, disease of an indeterminate duration, and chronic disease, respectively.[6] The mean seroconversion time is said to be 15 weeks after the clinical occurrence of hepatitis, with a range of 4 to 32 weeks.[4] Seroconversion occurring more than a year after exposure has been reported.[9] Such long time lags have important implications concerning follow-up in any seroprevalence study. Seroconversion rates also appear to be lower in patients with self-limiting disease, as opposed to those that progress to a chronic course. In a study in Japan, 20 of 22 patients with non-A, non-B hepatitis that progressed to chronicity were HCV-positive, while only 5 of 11 patients with self-limiting infections were positive ($P < .02$).[4] Moreover, the antibody response in those patients with self-limiting disease who do seroconvert is often more labile, declining and sometimes disappearing within a few years, whereas persistent levels are maintained in patients with chronic disease.[4] Along with the long time lag of seroconversion, this difference may indicate that there is insufficient antigen in patients with self-limiting infections to stimulate a detectable humoral response. Although it is conceivable that a different viral agent is involved, studies of animals have clearly shown that the same inoculum can lead to either chronic or self-limiting infections.[4]

Aside from its role in posttransfusion non-A, non-B hepatitis, HCV also appears to play an important role in nontransfusion-associated non-A, non-B hepatitis. This so-called sporadic form accounts for 10% to 25% of all cases of non-A, non-B hepatitis in the United Kingdom and nearly 50% in the United States.[10,11] In one US study, 34 of 59 patients (58%) with sporadic disease became HCV-positive at some stage after the occurrence of disease.[4] Similar studies in Germany and Italy have shown rates of 72% and 71%, respectively.[8,12] These last two rates compare with the 79% and 84% rate in transfusion-associated non-A, non-B hepatitis found in the same studies.

In contrast to the high seroprevalence rates found in the previous disease processes, the rate in the general population remains about 1%. Table 1 shows the prevalence of anti-HCV–positivity in blood donors in various countries. In addition to the composite rates shown for each country, there appear to be substantial regional variations within each particular country.

TABLE 1.—*Antihepatitis C Virus (HCV) Seroprevalence by Country*

Country	Population HCV-Positive, %	Source
United States	0.6	Williams and Dodd, 1990[6]
Japan	1.5	Williams and Dodd, 1990[6]
Canada	0.3	Williams and Dodd, 1990[6]
France	0.7	Janot et al, 1989[13]
Italy	0.9	Sirchia et al, 1989[14]
Germany	0.4	Kühnl et al, 1989[15]
Africa	6.0	Williams and Dodd, 1990[6]

Hepatitis C Virus and Primary Hepatocellular Carcinoma

Besides hepatitis, hepatitis C virus has been associated with other disease processes. The most important of these is primary hepatocellular carcinoma. Colombo and co-workers in 1989 reported the frequency of HCV-positivity in a group of patients with HBsAg-negative hepatocellular carcinoma to be 70%.[12] Likewise, Bruix and associates found an HCV-positivity rate of 81.4% in a group of patients with cryptogenic cirrhosis and hepatocellular carcinoma.[16] This association between HCV and hepatocellular carcinoma is usually recognized as the progression of chronic non-A, non-B hepatitis to cirrhosis and, finally, to carcinoma. Cirrhosis is not strictly necessary for the development of hepatocellular carcinoma, however. Studies have reported HCV-positivity rates as high as 40% in patients with hepatocellular carcinoma not associated with cirrhosis.[17]

There is also evidence that HCV may act synergistically with other agents already implicated in the development of hepatocellular carcinoma. In their study, Colombo and colleagues reported that 49 of 91 (54%) patients with HBsAg-negative hepatocellular carcinoma were both anti-HCV– and anti-HBcAb–positive, but only 26 of 139 (19%) patients with chronic non-A, non-B hepatitis were positive for both ($P < .001$).[12] In this study, the HCV-positivity rate in the carcinoma group was only 16% compared with the 55% rate in the non-A, non-B hepatitis group ($P < .001$), but the prevalence of anti-HBcAb was similar in both groups (9% versus 16%, not significant). These findings suggest that a previous HBV infection may enhance the potential for HCV to cause hepatocellular carcinoma. Such a previous HBV infection is not necessary for HCV-related carcinoma to develop, however. There are well-documented cases of HCV-related hepatocellular carcinoma in which sensitive polymerase chain reaction tests have shown no HBV DNA.[4] With regard to another cause, a Spanish study of patients with alcoholic cirrhosis with and without hepatocellular carcinoma showed HCV-positivity rates of 77% and 39%, respectively ($P < .02$).[16] The mechanism by which HCV causes hepatocellular carcinoma remains unclear. Incorporation into host DNA is unlikely because HCV replication does not appear to go through a DNA intermediate.

Hepatitis C Virus and Autoimmune Hepatitis

A study of 34 patients with chronic active autoimmune hepatitis showed a 44% prevalence of anti-HCV.[10] Similarly, Fusconi and co-workers found more than 80% of patients

TABLE 2.—*Antihepatitis C Virus (HCV) Seraprevalence in Various Risk Groups for Parenteral Exposure*

Risk Factor	Patients Studied, No.	HCV-Positive, %	Source
Hemophilia	756	70	Esteban et al, 1989[22]; Ludlam et al, 1989[23]; Noel et al, 1989[24]; Roggendorf et al, 1989[8]
Thalassemia	40	15	Williams and Dodd, 1990[6]
Dialysis	697	20	Williams and Dodd, 1990[6]
Intravenous drug use	236	70	Esteban et al, 1989[22]; Mortimer et al, 1989[25]; Roggendorf et al, 1989[8]

with type 2 autoimmune hepatitis to be seropositive.[18] The significance of this finding is unclear. It seems to suggest that HCV may act as an inciting factor in this disease process. This is particularly intriguing because the occurrence of autoimmune hepatitis is biphasic with respect to age, with many patients diagnosed later in life.[19] Such a pattern would be consistent with an environmental inciting agent. It is hypothesized that hepatocytes damaged by HCV may expose host antigens in such a way as to elicit an autoimmune response that persists even after the HCV infection itself has resolved. More study is clearly needed. McFarlane and associates have suggested that this high rate may merely represent false-positive results.[19] This thinking is based on their finding that although 20 of 31 patients (65%) with active autoimmune hepatitis were HCV-positive, only 1 of 22 patients in remission (5%) was positive ($P < .0005$). Furthermore, the optical density values observed from their assays were closely correlated with serum globulin ($r = .8846$, $P < .0005$) and immunoglobulin G ($r = .6281$, $P < .0005$) levels, and all the seropositive patients became seronegative when retested during remission. McFarlane and colleagues hypothesize that during active disease the anti-HCV assay may be detecting immunoglobulin G nonspecifically adhering to the ELISA plates.[19]

Transmission

The role of the parenteral transmission of HCV is well characterized in transfusions of blood or blood products. Cases of vertical transmission have also been reported,[10] as have cases of transmission by human bites.[20] Table 2 lists the HCV prevalence rates for various risk groups for parenteral exposure. Although transmission has been described in such cases, it remains unclear what the risk of a small parenteral exposure is. It is known that most patients with infections have low titers of 100 to 1,000 chimp infectious doses (CID) per milliliter.[4] Titers of as high as 1 million CID per ml have been obtained from acute-phase human serum specimens, however.[4] A recent report of 110 needle-stick exposures in medical personnel documented a 3.7% transmission rate.[21]

The route of transmission in sporadic cases is unclear. Epidemiologic studies have identified multiple heterosexual partners and sexual contacts as risk factors in persons with a history of hepatitis.[26] Table 3 shows the anti-HCV prevalence rates in various social risk groups. There is an increased prevalence of HCV-positivity in female contacts of intravenous drug abusers, and homosexual men who are positive for the human immunodeficiency virus (HIV) have a higher prevalence than homosexual men who are HIV-negative. Patients with sexually transmitted diseases likewise have increased rates. Hence, it is likely that HCV is transmitted through sexual contact. The risk of transmission, however, is apparently small. A nine-year cohort study of homosexual men by Melbye and co-workers found the cumulative incidence of HCV seroconversion to be 2.5% compared with 26% for HBV and 23% for HIV.[27] This suggests that HCV is about ten times less efficiently sexually transmitted than either HIV or HBV. In this study, variables in sexual life-style correlated with anti-HBcAb status but not with anti-HCV status.[27]

Casual contact transmission has also been suggested based on a report of HCV-positivity in 2 family members of 13 patients with chronic HCV disease.[4] A larger study by Everhart and associates failed to confirm this finding, however.[11] Interestingly, in their study, Hopf and colleagues found that of 62 cases of sporadic non-A, non-B hepatitis, 32 (52%) were in health care workers.[2] Finally, a role has also been suggested for arthropod vectors,[4] based on the fact that HCV is related to the family of togaviruses or flaviviruses, both of which are arboviruses. Arboviruses are a group of viruses usually transmitted by insect bites, and yellow fever virus, another arbovirus, is well recognized as a hepatotropic virus. In one case report, an insect vector was implicated in the clinical history of a patient with sporadic non-A, non-B fulminant viral hepatitis.[28]

Pathogenesis

It is currently unknown whether the hepatitis C virus is directly cytopathic to hepatocytes, as in the case of the hepatitis A virus, or causes damage by activating the immune destruction of infected cells, as in the case of the hepatitis B virus. The widespread changes often seen in infected tissue and the relative lack of lymphocytes in areas of damage suggest that HCV is directly cytopathic. On the other hand, the possible role of HCV in the pathogenesis of autoimmune hepatitis suggests that an immune mechanism may also be operative.

Several liver histologic features in patients with HCV hepatitis are not usually found in disease of other causes.[17] First, there are focally dense aggregates of lymphocytes in the portal areas. These infiltrates are also found within the sinusoidal space, in conjunction with Kupffer's cell hyperplasia. The bile duct epithelium is often abnormal and may mimic the lesions of primary biliary hepatitis. Although reported to be the least common finding, this is said to be the most important histologic marker for progression to chronicity.[17] These histologic findings are superimposed on those common to other types of viral hepatitis.

Fagan and Williams detected 60- to 70-nm viruslike particles with envelope surface proteins budding into the cell vacuoles of infected hepatocytes.[28] Also found were rod-

TABLE 3.—*Antihepatitis C Virus (HCV) Seraprevalence in Various Social Risk Groups*

Risk Group	Patients Studied, No.	HCV-Positive, %	Source
Women sex partners of intravenous drug users	8	12	Zuckerman, 1989[10]
Gay men	388	4.4	Williams and Dodd, 1990[6]
HIV-positive gay men	26	8	Zuckerman, 1989[10]

HIV = human immunodeficiency virus

shaped nuclear inclusions and cytoplasmic tubular structures consistent with the identification of HCV as an arbovirus.

Clinical Course

Posttransfusion non-A, non-B hepatitis has an incubation period of about 60 days and is known for its mild and often subclinical course.[29] Although cases of fulminant hepatic failure have been reported,[28] lethargy, anorexia, and occasional nausea are the usual presentations. Approximately 40% to 75% of patients remain completely asymptomatic, however, and the infection is recognized by the discovery of elevated serum aminotransferase levels. Such levels may peak just once, but most often they tend to fluctuate and may return to normal levels between exacerbations.[29] Jaundice is reported in only about 10% of patients and is usually mild.

Progression to chronic hepatitis, as defined by elevated serum aminotransferase levels for six months or more, occurs in about half of patients with acute hepatitis.[1] There is no good way of predicting when an acute case will progress to chronic disease. Of those patients in whom chronic disease develops, 20% will show morphologic features of cirrhosis within the decade after the acute illness.[1] Such changes usually evolve slowly over a period of decades, and the reported rates of cirrhosis increase with the duration of follow-up. Reinfection following the resolution of self-limiting disease has been reported.[4] Such cases have occurred after a second challenge with a large dose of the inoculum.

There is some question regarding the prognosis of sporadic, as opposed to posttransfusion, non-A, non-B hepatitis. Several studies in the United States, Italy, and Spain have shown posttransfusion non-A, non-B hepatitis to follow a more severe course than that of sporadic non-A, non-B hepatitis. Other studies in Germany, Switzerland, and Denmark have shown the opposite, however.[2] Hopf and colleagues found that whereas only 16% of patients with posttransfusion non-A, non-B hepatitis progressed to chronic active hepatitis or cirrhosis, 55% of those with sporadic non-A, non-B hepatitis did.[2] The significance of these differences remains unclear.

Treatment

Until recently, no therapy was shown to be effective against chronic non-A, non-B hepatitis. The use of corticosteroids, as well as the antiviral agent acyclovir, was shown to be ineffective.[33] Several randomized and controlled studies have now shown interferon alfa to be effective. Davis and associates, studying 166 patients with chronic posttransfusion non-A, non-B hepatitis, showed normal or near-normal serum alanine aminotransferase (ALT) levels in 46% of patients treated with interferon alfa-2B for six months compared with 8% of untreated controls ($P < .001$).[33] On biopsy, the treated patients also showed more regression of lobular and periportal inflammation ($P < .01$ and $P < .10$, respectively). Moreover, histologic improvement was not limited to those patients with a return to normal serum ALT levels, occurring as well in 13 of 25 (52%) nonresponding patients. A similar prospective study by Schvarcz and colleagues using the same treatment regimen for nine months showed normal ALT levels in 11 of 19 (58%) treated patients, compared with none of the 9 controls ($P < .001$).[34] This response to treatment does not appear to depend on a patient's anti-HCV status.[35] Furthermore, although anti-HCV antibody titers do not appear to change during therapy, there seems to be a dramatic reduction in serum HCV-RNA content after as little as four weeks of treatment.[36]

TABLE 4.—*Antihepatitis C Virus (HCV) Seroprevalence by Presence of Surrogate Markers for Non-A, Non-B Hepatitis**

Marker	*Patients, No.*	*HCV-Positive, %*
High ALT level	777	2.5
Positive for HBcAb	436	5.3
Both	60	37

ALT = alanine aminotransferase, HBcAb = hepatitis B core antibody

*From Williams and Dodd.[6]

Unfortunately, the discontinuation of therapy is associated with a high rate of relapse, as shown by elevated ALT levels. In the Davis study, 51% of responding patients had relapsed by six months,[33] and in the Schvarcz study, 64% had relapsed by six months.[34] A year after discontinuation, Di Bisceglie and co-workers found that 80% of responders had relapsed.[37] In general, those patients who relapse will respond if therapy is reinstituted.[34] Previous relapse rates do not include those patients who have a transient flare in serum ALT levels following the discontinuation of therapy.[33] Such a flare is reported to occur in as many as 36% of responders, and retreatment is not indicated in such patients.[33]

Prevention

Before the current anti-HCV assay was available, two surrogate markers were found to be associated with an increased risk of posttransfusion non-A, non-B hepatitis transmission. The routine screening of donor serum for ALT and anti-HBcAb resulted in a 50% decreased incidence of posttransfusion non-A, non-B hepatitis, with only a 5% loss in the blood supply.[6] Table 4 relates the HCV seroprevalence rates associated with each marker and shows the efficacy of screening.[6] The 37% HCV-positivity rate found when both markers are present appears to be relatively low. The cause of this lies in the long time lag associated with antibody development. Although infectious, a patient's serum may not be HCV-positive for more than six months. The current anti-HCV assays will therefore not obviate the need for surrogate marker screening.

Preliminary studies in the United States have implicated donors in the transmission of HCV hepatitis who were only HCV-positive and did not have either marker present. Investigators in Japan studied such donors and reported that of 21 recipients, non-A, non-B hepatitis developed in 16 (76%), with seroconversion occurring in 15 of those patients.[4] Of the other 5 recipients, 1 had preexisting HCV positivity, another already had chronic active hepatitis with cirrhosis at the time of transfusion, and 3 had demonstrable but nondiagnostic liver damage. Alter and associates predicted that routine donor screening would detect about 85% of transfusions capable of transmitting non-A, non-B hepatitis.[9] Those cases that are not identified would consist of recently infected donors who have yet to seroconvert and previously infected donors whose antibody responses have disappeared. We do not know whether seronegative donations from patients whose previous antibody response has disappeared remain infectious.[38]

There is currently some controversy regarding whether HCV-positive donated blood should be removed from the plasma pools used for the preparation of albumin, coagula-

tion factors, and immunoglobulins. Workers in France have advocated exclusion,[4] but the US Food and Drug Administration has decided not to screen until more is known about the effects of screening on the safety of the derived products.[39] Screening may not decrease the amount of virus in the pool but instead merely decrease the amount of antibodies against it.[39] Heating clotting factor concentrate or treating it with solvents or detergents results in the complete absence of seroconversion.[4]

Future Developments

Intense investigation is now under way regarding the development of better tests for HCV. Newer assays still based on the currently produced antigen, such as the recombinant immunoblot assay and modifications of the existing ELISA test, promise to offer better specificity. The current antigen, representing approximately 12% of the viral genome, does not bind a neutralizing antibody, and the current anti-HCV assays cannot distinguish between infectious and noninfectious HCV-positive serum specimens. Moreover, there are questions of poor specificity of the current assays in patients with other forms of chronic liver disease and in those with monoclonal gammopathies.[18,40]

Garson and co-workers recently developed a sensitive polymerase chain reaction method for the detection of HCV RNA that appears to provide good correlation with proved infectivity.[41] Further study of the now-characterized HCV genome promises the discovery of newer tests with better sensitivities and specificities, a better response in the acute phase of disease, and a better predictive value concerning which patients will have progression to chronic disease. Such study may also provide the basis for an as-yet-unavailable confirmatory test, as well as allow the discovery of a neutralizing antibody. This in turn may lead to a vaccine for HCV disease.

Although the ability to test for the hepatitis C virus has shown it to be the dominant cause of non-A, non-B hepatitis, there are instances where HCV cannot be identified. There is good evidence for at least one other agent being responsible for this form of hepatitis.[4] This agent is distinguished from HCV by its chloroform insensitivity. There may be others as well. It is interesting to note that Arima and associates in Okayama, working independently from researchers at Chiron Corporation but using similar techniques, isolated several clones that expressed polypeptides shown in an independent laboratory to react specifically with well-documented panels of non-A, non-B hepatitis serum.[42] These clones, however, do not appear to bear a relationship to any part of the HCV genome characterized at Chiron.[4] The importance of this finding is unclear at present.

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Epitomes

Important Advances in Clinical Medicine

Orthopedics

The Scientific Board of the California Medical Association presents the following inventory of items of progress in orthopedics. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome, and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, researchers, or scholars to stay abreast of these items of progress in orthopedics that have recently achieved a substantial degree of authoritative acceptance, whether in their own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Orthopedics of the California Medical Association, and the summaries were prepared under its direction.

Reprint requests to Division of Scientific and Educational Activities,
California Medical Association, PO Box 7690, San Francisco, CA 94120-7690

Tissue Banking

TISSUE STORAGE METHODS have included storage at 4°C for 12 to 24 hours, freezing at −170°C, freeze-drying, freeze-drying and partially decalcifying the bone, and various combinations of these techniques. If live cartilage or other live tissues are being transplanted, storage at 4°C is imperative. If only morselized bone is required, as in the filling of bone cysts found in spinal fusions or repairing nonunions, then freeze-dried and partially decalcified bone is recommended. If large bone allografts are needed for shape and strength, frozen allografts are recommended. Sterilely procured and processed frozen or freeze-dried allografts are recommended for ligament, tendon, and meniscus allografts.

The donor serum should be screened for communicable diseases that could be transmitted by the allograft. This requires a checklist and a donor evaluation form that satisfies the recommendations of the American Association of Tissue Banks. Particular attention should be paid at the time of donor autopsy to be certain that no pathologic disorder suggesting human immunodeficiency virus infection and no occult tumors are present. In addition, each specimen taken from the body should be cultured for contamination by bacteria.

The donor is maintained at 4°C from the time of death until the time of tissue procurement. The body is then taken to an operating department, where most donor procurements are done under sterile procedures. The extremity is prepared in the usual manner. Large skin incisions are made to expose the desired part, and the part is removed and wrapped in sterile towels after cultures have been done and it has been soaked in an antibiotic solution. It is then processed for storage.

Important medicolegal aspects should be noted during allograft procurement. For example, procurement represents processing a gift from the donor to the recipient. No charges should be made by the donor or the donor's family for the part to be transplanted, nor should they be charged for its tissue removal procedure. Although a tissue bank is responsible for the harvesting and processing of tissue, it is not responsible for the success of grafting.

JUAN J. RODRIGO, MD
Sacramento, California

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Medical Management of Spinal Cord Injury

IN THE PAST TWO DECADES, the ability to "decompress" an injured spinal cord from compressing structures and realign and stabilize the vertebral column with biomechanically sound spinal implants has improved dramatically. The initiation of early functional assessment and reactivation has provided patients with spinal cord injury the best possible physical environment for spinal cord recovery. Permanent spinal cord injury, however, will still be a reality for about 11,000 persons in the United States this year. The resulting paralysis is complicated by long-term psychological, social, medical, and economic ramifications.

The difficulty in substantially altering the neurologic dysfunction results from a lack of knowledge of the basic mechanisms involved in spinal cord injury. Recent investigations into the molecular nature of central nervous system ischemia have provided a wealth of information. Because most instances of spinal cord injury involve intact or crushed (rather than transected) ischemic spinal cords, the mechanisms of stroke and other intracranial ischemic lesions have been extrapolated and then expanded to spinal cord injury. These data have shown that a loss of intracellular energy stores rapidly leads to a loss of membrane integrity. Because a 10,000-fold calcium concentration gradient exists across the cell membrane, the accumulation of intracellular calcium is a major consequence of this metabolic derangement. This influx appears to occur through ion channels. Specifically, the *N*-methyl-D-aspartate (NMDA)-receptor calcium channel, activated by an ischemia-generated accumulation of glutamate within the synapse, is a major contributor. Neuron damage caused by this mechanism is called excitotoxicity. Once calcium enters the cell, phospholipases and proteases are activated, resulting in the production of damaging free radicals and the degradation of important cytoskeletal proteins such as neurofilaments.

Pharmacologic treatment has lagged behind discoveries on the mechanisms of injury. Based on studies of animals done in the early 1980s, a recent multicenter study carried out under the auspices of the National Acute Spinal Cord Injury Study has provided clear-cut evidence that administering high doses of methylprednisolone sodium succinate notably improved the neurologic outcome if given within the first eight hours after injury. The protective effect may be due to an inhibition of lipid peroxidation and neurofilament degradation. This randomized, controlled study is the first to

show a beneficial effect of any pharmacologic treatment of human spinal cord injury.

This work is encouraging, but in the past few years, a methodical search for agents that counteract the known effects of ischemia has provided compounds with more specific actions than corticosteroids. These agents are under extensive investigation using in vitro and in vivo trials in animals. The two types of compounds studied, NMDA-receptor antagonists and calpain inhibitors, act at different levels of the calcium cascade and may be synergistic. Other compounds have been developed to counteract the detrimental byproducts of lipid peroxidation. Thus, specific components of the cell derangement can be pharmacologically manipulated.

In the future, patients with spinal cord injury may be treated like those with myocardial infarction. Once the injury has occurred, rapid transfer to a specialized center with experience in the medical and surgical treatment of spinal cord injury will be standard. As the molecular nature of spinal cord injury becomes unraveled, compounds (or combinations of compounds) will be designed to counteract different levels of the ischemic cascade. This may prove extremely valuable in preserving neurologic function.

VANCE O. GARDNER, MD
VINCE CAIOZZO, PhD
Irvine, California

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Ilizarov Method

THE ILIZAROV METHOD is a technique that helps provide alternative solutions to some difficult orthopedic problems, including pseudarthroses, bone defects, angular and rotatory deformities, osteomyelitis, the correction of limb-length inequalities, enlargement of bones, lengthening of amputation stumps, arthrodeses of joints, and the management of open and closed fractures. The method has introduced a set of biologic principles that have recently been recognized and that require continued study.

Ilizarov's concept of "tension stress" posits that gradual controlled distraction stimulates bone production and neogenesis. When a distraction force is applied, tissue fibers and cells become oriented in the same direction as the distraction vector. This is said to mimic the process of natural growth. Certain factors are required for optimal bone regeneration. Stable fixation is necessary and is obtained with the Ilizarov apparatus. The rate and rhythm of distraction are also critical. The maximal rate at which the body can regenerate tissue is 0.25 mm four times a day for an overall rate of 1 mm a day. Unlike the Wagner technique, this gentle distraction allows bone to form without the need for supplemental bone grafting and internal fixation.

The Ilizarov apparatus comprises wires, fixation bolts, rings, threaded rods, hinges, and plates. These components allow the construction of more than 800 assemblies. The apparatus from a biomechanical aspect is stiff for bending and torsion but less stiff for axial loading, which is thought to help promote osteogenesis.

Preoperative planning is essential to apply the Ilizarov method successfully. Careful attention to "safe zones" during wire insertion is important to prevent damage to vital nerves and blood vessels. Placing the involved muscle compartment on stretch during wire insertion minimizes contractures. Careful attention is also required to adjust the skin so that there is no tension on the skin-wire interface. The wires are then fixed and tension applied to rings that are in turn connected by threaded rods. The Ilizarov frame can be constructed in a way that will allow the appropriate correction of the deformity or lengthening.

For bone lengthening, a corticotomy is made in the metaphyseal region. This is a low-energy osteotomy that preserves the periosteal envelope. A latency period is required postoperatively before distraction. New bone should be seen within three to four weeks once the distraction has begun. Once the correct length is obtained or angular deformity corrected, the apparatus remains in place until the consolidation phase has been completed. During the postoperative period, frequent visits are often required to adjust or modify the assembly. Once the goal has been achieved, the apparatus is removed on an inpatient or outpatient basis.

Special postoperative considerations are important, especially because the apparatus may be in place for as long as a year. Pain tends to be mild to moderate, but its duration may make management a challenge. Intensive physical therapy and splinting techniques are used to prevent flexion contractures of the surrounding joints. Psychological support and family counseling are key elements to successful treatment.

Postoperative problems can include pin-track infections, premature or delayed consolidation, joint contractures, and pin breakage that may require replacement.

The Ilizarov method provides orthopedic surgeons with another tool to manage difficult problems. It is complex yet provides hope for some patients. Its use should be reserved for centers with extensive experience in pediatric or reconstructive orthopedics until more data are available regarding techniques, complications, and results.

KEVIN W. LOUIE, MD
San Francisco, California

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Update on the Diagnosis and Treatment of Scaphoid Fractures

THE SCAPHOID SERVES as an important mechanical link between the proximal and distal rows of carpal bones. Nonunion or malunion following its fracture allows malalignment of the carpal bones among themselves and against the radius. This predisposes to degenerative arthritis. Changes develop insidiously but predictably 10 to 20 years later. This accounts for the emphasis being placed on precise anatomic healing of the scaphoid. Only then can normal mechanics of the wrist be restored and late degenerative changes be avoided.

Because of the scaphoid's oblique orientation in the wrist in both the frontal and sagittal planes, routine wrist x-ray films may not always reveal a fracture line. Undiagnosed fractures are the most common cause of nonunion. When a fracture is suspected but initial radiographs are normal, placing the wrist in a cast for two weeks and repeating the examination and radiographs are indicated. If scaphoid tenderness persists but the radiographs remain normal, bone scanning using technetium Tc 99m will identify the occult fracture. For nondisplaced fractures, a thumb spica cast should be in place until tenderness has subsided and radiographic healing is evident. This usually takes 9 to 12 weeks. Orthopedists debate whether long-arm or short-arm casts should be used for nondisplaced scaphoid fractures; most would agree to at least several weeks of long-arm casting for a displaced fracture that has been successfully reduced by manipulation.

Because more than 1 mm of fracture displacement or any angular malalignment will predispose the wrist to degenerative changes, computed tomography oriented along the scaphoid's long axis is often useful to verify anatomic reduction. If anatomic alignment cannot be accomplished and maintained by closed means, then open reduction is necessary. Kirschner wire fixation has been used, but this requires a protective cast and has the risks of pin-track infection and wrist stiffness related to the prolonged immobilization. Internal fixation can be done with the Herbert screw, which is specifically designed for scaphoid fractures and nonunions. Rather than a conventional screw head, the trailing shaft supports threads that are more shallowly pitched than those on the leading shaft. Thus, the screw can be completely buried in the bone to avoid touching adjacent articular surfaces. More important, the pitch differential between the leading and trailing ends allows compression of the bone fragments as the device is inserted. Bone healing is not necessarily accelerated with the use of the screw, but the time of cast immobilization is lessened, reducing disability and the risk of wrist stiffness.

Despite adequate primary treatment, about 5% of scaphoid fractures fail to unite. This discouraging result is usually related to a disruption of the proximal fragment's blood supply at the time of injury. Even for scaphoid nonunions that are asymptomatic, further efforts should be directed at achieving union to avoid osteoarthritic changes several decades later. Electrical stimulation is not useful, and partial or total silicone replacement arthroplasty risks a foreign body synovitis from the debris particles generated. Autogenous bone grafting remains the treatment mainstay. The bone graft stimulates bone healing across the nonunion site. Also, a properly shaped graft restores the anatomic contour of the scaphoid. Here, as with acute fractures, a reconstructed scaphoid can be stabilized either with Kirschner wires and a cast or with the scaphoid screw. In patients who have residual pain with equivocal healing seen on plain radiographs, computed tomography again has proved a useful diagnostic and treatment guide.

ROY A. MEALS, MD
Los Angeles, California

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Open Reduction of Pelvic Fractures

TREATING PELVIC FRACTURES nonoperatively has been associated with poor long-term results in certain types of pelvic injuries. These injuries include displaced fractures of the acetabulum in which joint incongruity is produced by the injury, leading to a rapid, progressive, posttraumatic degenerative disease of the hip joint, and injuries to the pelvic ring between the acetabulum and the sacrum, causing either rotatory or vertical instability of the injured hemipelvis. Such instability may lead to nonunion of the fracture, unacceptable rotational deformity, or unacceptable shortening of the hemipelvis and limb. Indications for the nonoperative treatment of acetabular fractures include a fracture displacement of less than 3 mm, low anterior column or transverse type fractures, both column fractures with secondary congruence, and fracture with mild displacement in an elderly person. Fractures with displacement of 3 mm or more and high acetabular fractures are generally treated with open reduction and internal fixation. Fractures in elderly patients may qualify for open reduction and internal fixation because of their displacement or location. The operative procedure is a major one, however, and a better result may often be achieved by early nonoperative treatment followed by total hip arthroplasty if symptoms so warrant.

The techniques of open reduction and internal fixation of acetabular fractures are technologically complex and require a relatively long "learning curve." Common complications include heterotopic ossification, often treated with indomethacin, low-dose irradiation, or both, and degenerative arthritis due to the inability to restore anatomicity of the joint or damage to the articular cartilage caused by the initial injury.

Pelvic ring injuries require fixation when they are unstable. For a rotationally unstable injury with overriding or widening of the symphysis pubis but with intact posterior sacroiliac ligaments, an anterior symphysis plate or an anterior iliac crest external fixator will usually suffice. Vertically unstable fractures have both anterior and posterior disruption and require internal fixation if the vertical displacement of the hemipelvis is more than 1 cm. Posterior iliac crest fractures and disruptions of the sacroiliac joint can be fixed by using either plates or lag screws. Sacral fractures occasionally require the use of the cobra plate or sacral bars. Supplemental anterior fixation using an external fixator or a symphysis pubis plate increases the biomechanical stability of the fracture fixation.

Complications of open reduction and internal fixation of pelvic ring fractures include the possibility of spermatic cord injury with symphysis pubis plating, neurologic injury with overcompression of the neural foramina of the sacrum or with the anterior approach to the sacroiliac joint, and posterior wound breakdown, seen in approximately 26% of cases involving posterior surgical approaches to the sacroiliac joint. Newer techniques of internal fixation of both acetabular and pelvic ring fractures include the use of manipulation and traction for closed reduction, followed by lag screw percutaneous fixation under image intensification or computed tomography.

ROBERT BAIRD, MD
Orange, California

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Bearing Surfaces in Total Joint Replacement

THE DESTRUCTIVE EFFECTS of wear and wear debris have challenged the existence of joint replacement. Charnley's initial use of polytetrafluoroethylene (Teflon) resulted in severe destructive granulomas from the Teflon debris. High-density polyethylene at this time continues to be the most used of all substitute bearing materials, but problems with it have now begun to emerge. Many now think that osteolysis is as much related to wear debris as it is to cement fragmentation. The term "cement disease" is considered a misnomer; it should be particle disease.

Attempts are being made to improve the high-density polyethylene as a joint surface material, changing the physical structure by altering its molecular chains. This new material seems to have superior properties when creep, oxidation, fracture, pitting, delamination, and wear are tested in the laboratory. It is unknown if this material will decrease the amount of wear debris when it is used clinically in patients.

Titanium alloy should not be used as an articular surface in joint replacement. Titanium alloy loses its polished surface when articulating against polyethylene and generates particulate debris that produces osteolysis, thus making it ill-suited as a bearing surface for joint replacement. A new process of nitrogen ion bombardment of titanium is being developed and used, but its clinical usefulness is unknown.

Ceramic on ceramic-bearing components also appears to generate considerable particulate debris, and caution must be exercised before this combination is used. Ceramic heads, articulating with polyethylene, have been shown to have superior wear characteristics and thus generate less particulate debris. Time will tell whether the incidence of lysis is affected by ceramic on polyethylene, thus justifying the expense of the ceramic heads.

In addition to the materials chosen, the size of the femoral head is important in joint replacement. The 28-mm head, or midrange head prosthesis, seems to be the best compromise when linear wear and volumetric wear are considered. This head size, though, must be placed in proportion to the patient and the amount of polyethylene in the bearing.

RICHARD B. WELCH, MD
GARY LEVENGOOD, MD
San Francisco, California

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Arthroscopic-assisted Reconstruction of the Anterior Cruciate Ligament

RUPTURE OF THE ANTERIOR CRUCIATE LIGAMENT can lead to degenerative arthritis of the knee. Persons who participate in sports that require jumping and pivoting are at a high risk for injury leading to repeated episodes of instability, and surgical reconstruction is usually undertaken. Although no procedure can exactly replicate the kinematic and anatomic properties of the anterior cruciate ligament, intra-articular reconstruction with a strong and isometric graft offers the best hope of restoring anatomic and functional stability and preventing future degenerative changes.

Traditional intra-articular reconstruction is associated with substantial morbidity from the surgical dissection necessary to expose the torn anterior cruciate ligament and then implant the substitute. In most cases, this has meant severe pain, swelling, and difficulty initiating range-of-motion exercises in the immediate postoperative period, resulting in a hospital stay of three to five days.

Arthroscopic techniques have recently been used to reconstruct the anterior cruciate ligament by adding a small extracapsular incision along with routine arthroscopic portals. This procedure is often done on an outpatient basis, and usually only an overnight hospital stay is required. With diminished pain, range of motion can be regained early. The cosmetic advantage of arthroscopic-assisted reconstruction of the anterior cruciate ligament is obvious.

The arthroscopic procedure begins with the use of a motorized shaver and burr to remove remnants of the torn ligament and to enlarge the intercondylar notch of the femur to prevent impingement of the graft as the knee extends. A special aiming guide allows a tunnel to be drilled into the joint at the selected tibial attachment site. Work is carried out through this tunnel while viewing arthroscopically, and the femoral attachment site is selected. A strain gauge is used to measure any shortening or elongation between the selected points. If substantial strain is found, the femoral attachment site can be altered. Once an acceptable site is located, the bony tunnel for the anterior cruciate ligament graft is drilled from within the joint, using the tibial tunnel as a working portal. The selected graft (usually autogenous tissue) is then passed through the tibial tunnel, across the joint, and positioned in the closed femoral tunnel. After the graft is securely fixed, immediate range of motion is allowed.

Regardless of the method of reconstruction, all biologic grafts used to reconstruct the anterior cruciate ligament undergo revascularization that requires protection of the graft from excessive activity for several months. Despite the improved cosmetic and perioperative advantages of arthroscopic reconstruction, the long-term outcome is similar to the results achieved by open methods.

RICHARD A. MARDER, MD
Sacramento, California

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Percutaneous Discectomy

PERCUTANEOUS LUMBAR DISCECTOMY is a safe and effective alternative to laminectomy in some patients who require discectomy for the treatment of herniated nucleus pulposus. Percutaneous discectomy is done under local anesthesia and fluoroscopy with the patient in the lateral decubitus or prone position. The procedure has fewer potential postoperative difficulties than laminectomy or chemonucleolysis, with no epidural scarring, allergic reactions, or serious neurologic complications.

Patient selection is extremely important. The criteria for selection should be strict and include the following: the patient must have shown no improvement after at least six weeks of conservative therapy; the primary complaint is sciatica—that is, leg pain is greater than back pain; paresthe-

sias or hyperesthesia occurs in a specific dermatome or dermatomes; straight-leg raising is restricted, preferably less than half of normal; weakness, atrophy, sensory changes, or reflex alteration is demonstrated in a lower extremity; and the findings of computed tomography, myelography, or magnetic resonance imaging correlate with clinical findings.

Absolute contraindications include causes of symptoms such as tumor, infection, spondylolisthesis, or congenital abnormalities; sequestration or a free fragment; foraminal stenosis; and severe facet arthropathy. Relative contraindications are back pain without sciatica, previous chymopapain injection at the same level, stenosis or facet arthropathy with disc protrusion, multiple levels, and internal disc derangement. These relative contraindications constitute a "gray zone" for surgeons.

The procedure is done with either manual instruments, such as pituitary rongeurs, or an automated suction aspiration probe called the nucleotome. The procedure consists of inserting a cannula through a small incision down to the annulus by a posterolateral approach. This avoids entering the spinal canal and injuring its contents. The instrument—rongeur or nucleotome—is then inserted into the disc for the removal of nucleus pulposus material. Positioning of the instruments is carefully monitored by fluoroscopy throughout the procedure.

The following five criteria should be met for the procedure to be considered a success: no further intervention is needed; radicular pain has moderately or totally improved; postoperative function has improved; no need for narcotic analgesics exists; and both patient and surgeon are satisfied.

The percutaneous discectomy procedure is a safe and well-tolerated alternative to laminectomy with discectomy or chemonucleolysis in patients meeting the selection criteria. With these patients, it is reasonable to expect a success rate in the range of 70% to 75%.

JAMES M MORRIS, MD
San Francisco, California

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Objective Measurements for Rehabilitation After Back Injury

WE NEED OBJECTIVE MEASUREMENTS of spinal function after back injury to know if a patient is improving with treatment or has reached a plateau. Once a plateau has been reached with an exercise program, the level of impairment can be identified and job readiness established.

There are two important elements to measure: range of motion and muscle performance. In the lumbar spine, the spinal range of motion is difficult to separate from hip range of motion. Pelvic rotation must be separated from lumbar motion. The current American Medical Association guidelines recommend the use of two inclinometers to identify true lumbar range and the range of the thoracic or cervical spine.

An array of computerized devices to measure range and strength has entered the marketplace. The most accurate measurements can be obtained when the equipment can isolate spinal segments as well as stabilize the pelvis. One system collects data simultaneously along three axes—flexion-extension, rotation, and lateral bend. This device monitors both speed and strength. Strength screening can be accomplished on the equipment at variable speeds. At present, there is no evidence that exercise training at various speeds offers an advantage for muscle strengthening.

The controlling of speed during testing is known as isokinesis. If speed is controlled by the equipment when the patient is tested, high-impact forces occur as the patient tries to make the machine move faster. Isokinetic testing is dynamic testing, and thus gravity and inertia must be controlled for. Comparisons among populations of patients are not always accurate and reliable.

In addition to the variable-axes and the speed-controlled equipment, a third method of measuring range and muscle performance of the spine is available. This equipment measures isometric strength at various equidistant points along the arc of available range. To evaluate spinal function only, the spine is isolated from the pelvis and extremities when the patient sits in the equipment. Strength training through slow variable-resistance exercise in a concentric and an eccentric mode is also available. Function measured in this manner is the most accurate, and strength training is the most efficient.

Range and muscle strength can now be tested with commercially available computerized equipment. Valid results are variable for most equipment, but experience has shown that measuring function rather than documenting pain allows the best opportunity for an efficient rehabilitation program.

VERT MOONEY, MD
San Diego, California

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Alerts, Notices, and Case Reports

Superior Mesenteric Artery Thrombosis Associated With Antiphospholipid Syndrome

MAURICE E. HAMILTON, MD
Sacramento, California

THE ASSOCIATION of antiphospholipid antibodies (anticardiolipin antibodies, the lupus anticoagulant, and reagin) with thrombosis, recurrent fetal loss, and thrombocytopenia has recently been classified as the antiphospholipid syndrome.[1-8] Thrombotic events associated with this syndrome most often involve the venous system, especially the deep veins of the leg, but also the renal vein, hepatic vein, portal vein, pulmonary vein, and inferior vena cava.[2,4,7,8] Arterial thrombosis may also occur, affecting the cerebral, coronary, renal, and retinal arteries.[3,4,7,8] Only rarely has mesenteric artery thrombosis been noted.[9,10] This report describes thrombosis of the superior mesenteric artery leading to small bowel infarction in a woman with the antiphospholipid syndrome.

Report of a Case

The patient, a 29-year-old woman, was admitted to the hospital because of nausea with progressively worsening epigastric and lower abdominal pain of four days' duration. An upper gastrointestinal series done the day before admission was normal. Nausea and abdominal pain first developed four months earlier, at which time gastroduodenoscopy revealed gastritis, duodenitis, and a duodenal ulcer. These symptoms resolved during therapy with cimetidine.

The patient had a history of migraine headaches. Proteinuria (2+) was noted on routine urinalysis two years before admission; urinary protein excretion was 5.4 grams per 24 hours the month before admission. A biologically false-positive serologic test for syphilis was detected ten years previously. The patient was married without children. She had had five spontaneous abortions, always occurring during the first trimester, most recently four months before admission. She was placed on a regimen of an oral contraceptive—norgestrel and ethinyl estradiol—after the last abortion. She smoked a pack per day of cigarettes.

On admission her temperature was 37.6° C. The abdomen was diffusely tender without organomegaly or abnormal masses. Erythematous macules and subsequently livedo reticularis were noted on the palms. The physical examination revealed no other abnormalities. Laboratory test results included a leukocyte count of 11.6×10^9 per liter (11,600 per μl) with normal differential count, hematocrit 0.34 (34%), platelet count 170×10^9 per liter (170,000 per μl), sedimentation rate 58 mm per hour, serum albumin 33 grams per liter (3.3 grams per dl), and serum creatinine 70 μmol per liter (0.8 mg per dl). A urinalysis showed 4+ protein with many granular and hyaline casts. A plain x-ray film and computed tomographic scan of the abdomen were normal. Endoscopy showed mild gastritis; the duodenal mucosa was friable with a mottled, granular appearance. A superficial ulceration was present in the third portion of the duodenum; a biopsy of the duodenum revealed no definite abnormalities. Barium enema was normal.

On the seventh hospital day the patient had severe abdominal pain associated with a rigid abdomen and a temperature of 39.9° C. An exploratory laparotomy revealed infarction of most of the jejunum and ileum; the superior mesenteric artery was hard with no pulse. About 200 cm of jejunum and ileum was resected, leaving the proximal 68 cm of jejunum and the terminal 3 cm of ileum. An activated partial thromboplastin time was prolonged (patient, 42.9 seconds; control, 26 seconds) and failed to correct following the addition of an equal amount of normal plasma; the prothrombin time was normal. The platelet count decreased to 38×10^9 per liter.

High-dose corticosteroid therapy was administered. The patient was anticoagulated with heparin for presumed antiphospholipid syndrome. Total parenteral nutrition was instituted. During a second laparotomy the next day, an additional 8 cm of distal jejunum appeared nonviable and was resected; the gross appearance of the remaining bowel had improved. Histologic examination of the specimen of bowel showed areas of mucosal necrosis but no evidence of vasculitis (Figure 1). Over the next several days, the thrombocytopenia resolved and the palmar rash faded. No further bowel resection was required.

Because of increasing proteinuria (13.8 grams per 24 hours), a renal biopsy was taken on the 18th hospital day. This showed mild to moderate focal mesangial cell hyperplasia with focal segmental glomerular staining for immunoglobulin (Ig) M, C3, C1q, properdin, and fibrin(ogen), characteristic of focal segmental glomerulosclerosis (Figure 2). No electron-dense deposits were detected.

Serologic studies done before corticosteroid therapy was initiated revealed a high level of IgG anticardiolipin antibody (16 standard deviations above normal) without IgM or IgA anticardiolipin antibody. A C4 level was mildly decreased—0.11 grams per liter (11 mg per dl; normal >0.15 grams per liter)—but total hemolytic complement (CH_{50}) determina-

Figure 1.—The intestinal artery appears normal, without evidence of vasculitis (original magnification × 200, hematoxylin and eosin stain) (prepared by David Jensen, MD).

(Hamilton ME: Superior mesenteric artery thrombosis associated with antiphospholipid syndrome. West J Med 1991 Aug; 155:174-176)

From the Division of Rheumatology, Allergy, and Clinical Immunology, University of California, Davis, Medical Center, Sacramento.

Reprint requests to Maurice E. Hamilton, MD, 534 East Pine St, Suite B, Stockton, CA 95204

ABBREVIATIONS USED IN TEXT

Ig = immunoglobulin
SLE = systemic lupus erythematosus

tion was normal. Circulating anti-DNA antibody was present in low quantity (260 IU per ml; normal < 160 IU per ml). A rapid plasma reagin test was positive, and microhemagglutination assay for *Treponema pallidum* antibodies was negative. The following tests were normal or negative: antinuclear antibody, rheumatoid factor, cryoglobulins, C1q binding assay, Coombs' test, antithrombin III, protein C, protein S, factor VIII, and factor IX. Subsequent C4 and anti-DNA determinations were normal. No IgG anticardiolipin antibody was detected a month after initiating methylprednisolone sodium succinate therapy, but IgM anticardiolipin antibody was noted at that time. The IgG anticardiolipin antibody reappeared as the corticosteroid dosage was tapered and discontinued.

We have now had the opportunity to observe the patient for four years following the bowel infarction. Her IgG anticardiolipin antibody has returned to a high level, and she remains anticoagulated with warfarin sodium therapy. She has had no evidence of recurrent thrombosis, and her renal status is stable. She receives 1,700 calories of parenteral nutrition on alternate days to supplement her oral caloric intake.

Comments

Mesenteric artery thrombosis as a manifestation of the antiphospholipid syndrome has been documented rarely. This article appears to be the first report of superior mesenteric artery thrombosis associated with bowel infarction in a patient with the antiphospholipid syndrome. Thrombosis of the inferior mesenteric artery and splenic artery necessitating colectomy and splenectomy has been reported in a 44-year-old woman with systemic lupus erythematosus (SLE) and antiphospholipid antibodies.[9] In addition, the case of a 53-year-old man with antiphospholipid antibodies and occlusion of several abdominal arteries, including the mesenteric arteries, has been described.[10]

Figure 2.—A glomerulus stained for fibrinogen shows prominent staining of peripheral segmental areas, characteristic of focal segmental glomerulosclerosis (original magnification × 285, fluorescein isothiocyanate-conjugated anti-fibrin[ogen] stain) (prepared by Charles N. Gamble, MD).

The patient in this report also showed other features of the antiphospholipid syndrome. Her proteinuria was caused by focal segmental glomerulosclerosis, a lesion associated with glomerular thrombosis in SLE patients with the lupus anticoagulant.[11] Spontaneous abortions, noted five times in this patient, have been linked to the presence of antiphospholipid antibodies, which may predispose to placental thrombosis and infarction.[12-14] Thrombocytopenia, livedo reticularis, and migraine headaches are additional manifestations of this syndrome noted in our patient.[15-17]

Anticardiolipin antibody, lupus anticoagulant, and reagin, representing related but nonidentical antiphospholipid antibodies, were all detected in this patient. Several investigators have reported a correlation between the presence of IgG anticardiolipin antibody and antiphospholipid syndrome, although IgM and IgA anticardiolipin antibodies have also been associated with this syndrome.[5,7] When initially tested, our patient showed only IgG anticardiolipin antibody. After the administration of high-dose corticosteroid therapy, only IgM anticardiolipin antibody was detected; after the discontinuation of corticosteroids, a high level of IgG anticardiolipin antibody reappeared. Whether corticosteroid therapy resulted in the differential expression of these isotypes is speculative.

Antiphospholipid antibodies have been described most often in patients with systemic lupus erythematosus, with recent studies reporting these antibodies in 30% to 40% of SLE patients.[7,18,19] Patients with the antiphospholipid syndrome often display features of lupus but lack circulating antinuclear antibody.[18] Our patient was typical of this group: she fulfilled 3 of the 11 criteria for the classification of SLE—proteinuria, thrombocytopenia, and immunologic disorder (a biologically false-positive test for syphilis)—but had negative antinuclear antibody determinations.[20] Indeed, some data suggest that patients with the most serious manifestations of antiphospholipid syndrome are within this antinuclear antibody-negative group.[18] Antiphospholipid antibodies may also develop following the ingestion of drugs such as chlorpromazine and in association with malignant neoplasms and infections, including the acquired immunodeficiency syndrome.[4,21]

The mechanism predisposing to thrombosis in the antiphospholipid syndrome is unknown. Antiphospholipid antibodies may directly activate platelets by binding to membrane phospholipids, leading to platelet aggregation and thrombosis.[15] Alternatively, antiphospholipid antibodies may bind to phospholipids in the membrane of endothelial cells, causing decreased production of prostacyclin (increasing platelet aggregation) or decreased release of plasminogen activator (decreasing fibrinolysis).[22,23] Moreover, plasma from patients with the lupus anticoagulant has been reported to inhibit prekallikrein activity, suggesting another possible cause of decreased fibrinolysis leading to thrombosis.[24]

The differential diagnosis of hypercoagulable states includes abnormalities of coagulation proteins, such as deficiency of protein C, protein S, or antithrombin III; levels of these proteins were normal in this patient. The nephrotic syndrome may predispose to thrombosis due to urinary loss of antithrombin III or to hypoalbuminemia, which may lead to increased platelet aggregation.[25,26] As the antithrombin III level in our patient was normal and the degree of hypoalbuminemia initially noted was mild, it seems unlikely that nephrotic syndrome contributed significantly to her throm-

bosis. It is noteworthy that our patient started using an oral contraceptive only months before the diagnosis of mesenteric artery thrombosis. Asherson and colleagues recently reported that ten patients with antiphospholipid antibodies had thrombosis or other complications develop while they were taking oral contraceptives.[27] Whether smoking contributed to the thrombosis described in this patient is uncertain.

The treatment of thrombosis from antiphospholipid syndrome is anticoagulation. The importance of continuing anticoagulant therapy in patients with thrombosis and persistently high anticardiolipin antibody levels has been emphasized.[28] The role of corticosteroid therapy appears to be limited, but it has been used in patients with recurrent thrombotic events despite anticoagulation and in extremely ill patients.[4,29] Plasmapheresis combined with the use of cyclophosphamide has been proposed as adjunctive therapy for patients with devastating vasculopathy.[29]

In summary, a young woman with several manifestations of the antiphospholipid syndrome presented with jejunal and ileal infarction requiring resection of most of the small intestine. After four years' follow-up, the patient remains anticoagulated without evidence of recurrent thrombosis but with a high level of IgG anticardiolipin antibody. Measurement of antiphospholipid antibodies is indicated in the evaluation of clinical manifestations consistent with antiphospholipid syndrome, including thrombosis, recurrent fetal loss, and thrombocytopenia.

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Metastasis-induced Acute Pancreatitis

SHAUN S. J. HUNG, MD
BACH ARDALAN, MD
Miami, Florida

THE COMMON CAUSES of acute pancreatitis include alcoholism, biliary tract disease, trauma, surgical therapy, hyperlipidemia, hypercalcemia, and infections. In addition, acute pancreatitis can be induced by chemotherapy,[1,2] tumor lysis,[3] or tumor itself in patients with malignancy. The association of pancreatitis and pancreatic carcinoma is well recognized. Of 255 consecutive patients with pancreatic or ampullary carcinoma, significant pancreatitis by histologic criteria was present in 26.[4] Metastatic lesions of the pancreas have been reported from a wide variety of primary tumors[5]; those associated with clinical pancreatitis are rare, however. Chowhan and Madajewicz documented a 3.3% incidence,[6] and Yeung and colleagues reported a 7.5% incidence of metastasis-induced acute pancreatitis in patients with small-cell lung cancer.[7] Similarly, McLatchie and Imrie reported only 7 cases due to metastasis among 360 patients with acute pancreatitis seen during a six-year period.[8] The objectives of this study are to report this incidence in a county hospital and to review the literature on this disorder.

Patients and Methods

The medical records of all patients discharged from Jackson Memorial Hospital, Miami, Florida, between January 1980 and December 1987 with a diagnosis of primary nonpancreatic malignancy and acute pancreatitis were reviewed retrospectively. A histology-proven malignant disorder was

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From the Department of Oncology, University of Miami School of Medicine, Florida. Dr Hung is now with the Department of Medicine, Kaiser Permanente Medical Center, Santa Clara, California.

Reprint requests to Shaun S. J. Hung, MD, Department of Medicine, Kaiser Permanente Medical Center, 900 Kiely Blvd, Santa Clara, CA 95051.

TABLE 1.—*Metastasis-induced Acute Pancreatitis in 5 Men*

Patient	Age, yr	Primary Tumor	Tissue Diagnosis	Therapy	Survival†	Cause of Death
1	54	Lung adenocarcinoma	Autopsy	Conservative*	3 d	Lung cancer
2	74	Stomach adenocarcinoma	Autopsy	Conservative*	3 d	Pancreatitis; pneumonia
3	55	Hepatocellular carcinoma	Autopsy	Conservative*	1 d	Hemorrhagic pancreatitis
4	75	Liver angiosarcoma	Laparotomy	Conservative*	1+ mo	Lost to follow-up
5	25	Diffuse large-cell lymphoma	None	Abdominal irradiation	2 mo	Lymphoma

*Conservative measures included nasogastric tube suction, intravenous fluids, and the use of analgesics.
†Duration of survival was measured from the clinical onset of pancreatitis to the time of death (patients 1, 2, 3, and 5) or the last follow-up visit (patient 4).

needed for entry in this study. The diagnosis of acute pancreatitis was based on clinical, laboratory, and radiologic findings. Although histologic examination of the pancreas was not required for this analysis, it was made in about half of the patients. When pancreatic biopsy or necropsy was not done, the determination of the cause of pancreatitis was based on clinical and radiologic findings.

Results

A total of 28 patients were discharged with the diagnosis of primary nonpancreatic malignancy and acute pancreatitis during the eight-year period. Six patients were excluded from analysis because medical records were not available in three cases and no tissue diagnosis of malignancy was made in the other three. The causes of acute pancreatitis in the remaining 22 patients include metastasis (5 patients), alcoholism (4), abdominal operation (3), cholelithiasis (2), infection (2), L-asparaginase (1), and idiopathic (5). Four of the five patients with metastasis-induced pancreatitis (Table 1) had microscopic evidence of pancreatic (patients 2, 3, and 4) or peripancreatic (patients 1, 2, and 4) invasion by tumor, and no other etiologic factors of acute pancreatitis could be identified. Although the fifth patient with non-Hodgkin's lymphoma did not have a histology-proven pancreatic metastasis, the clinical and radiologic findings and a partial response to abdominal irradiation are consistent with a lymphomatous process.

Report of a Case

The patient was a 25-year-old man admitted for epigastric and periumbilical pain radiating to the back for two weeks. Eleven months before admission, he was diagnosed with stage II diffuse large-cell lymphoma in the neck and mediastinum and received chemotherapy consisting of cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, prednisone, bleomycin sulfate, and methotrexate. Because the disease in the chest continued to progress, he underwent thoracic irradiation, 15 grays (1,500 rads) in ten fractions, one month before admission. There was no history of alcohol abuse.

On physical examination his abdomen was soft but diffusely tender. Laboratory tests elicited the following values: leukocyte count, 9.3×10^9 per liter (9,300 per μl); blood urea nitrogen, 1.4 mmol per liter (4 mg per dl); creatinine, 62 μmol per liter (0.7 mg per dl); calcium, 2.27 mmol per liter (9.1 mg per dl); and amylase, 260 units per liter (normal 30 to 110). The results of liver function tests were all within normal limits. A computed tomographic scan of the chest and abdomen showed a left mediastinal mass, periaortic and inguinal lymphadenopathy, and an extensive and lobulated mass in the celiac and peripancreatic regions inseparable from the head of the pancreas. After conservative management, he was discharged five days later with an amylase level of 196 units per liter.

Two weeks after discharge, the patient was readmitted with similar symptoms and signs, and the serum amylase level was 244 units per liter. He was treated with abdominal irradiation, 20 Gy in 20 fractions. When radiotherapy was completed, the abdominal pain was partially relieved and the amylase level was 33 units per liter, but he died three weeks later because of progressive lymphoma. An autopsy was not done.

Discussion

Metastasis-induced acute pancreatitis is a rare occurrence, and over an eight-year period, we saw only five such cases in a hospital serving the Dade County, Florida, area. Metastases, however, accounted for 5 (23%) of the 22 incidents of acute pancreatitis in patients with primary nonpancreatic malignancy. In all, 29 other cases of this disorder have been reported in the English literature, and these tumors include bronchogenic carcinoma (12 patients),[6-13] lymphoma (10),[14-22] gastric carcinoma (5),[8] melanoma (1),[23] and anaplastic carcinoma of the tonsil (1).[8] Two of our patients (3 and 4) had hepatocellular carcinoma-induced and hepatic angiosarcoma-induced pancreatitis, respectively, which have not previously been reported.

The mechanisms of this disorder include pancreatic ductal obstruction or rupture following either direct tumor invasion or peripancreatic lymph node involvement and vascular compromise by neoplastic destruction or encasement of pancreatic vessels.[7] It may be the presenting feature of a malignant neoplasm[6,8,9,11-13,15-22] or the first evidence of metastasis[10,23] or recurrence.[7,14] Distinguishing between acute pancreatitis due to metastasis and acute pancreatitis of other causes could be difficult because the clinical presentations are similar in many respects and laboratory tests are not of much use in the differential diagnosis. Neither abdominal ultrasonography nor computed tomographic scan is definitive because metastases may be extensive or associated with secondary pancreatitis and pancreatitis of other causes could be focal. Unless clinical and radiologic findings clearly indicate the presence of pancreatic or peripancreatic metastases, a histologic diagnosis may be needed if clinical pancreatitis has not resolved after conservative management and antitumor therapy is contemplated. Percutaneous fine-needle aspiration of the pancreas is a useful procedure with a sensitivity ranging from 48%[24] to 85%,[25] and the risk and discomfort are minimal. Normal findings do not rule out the presence of metastases, however. If effective therapy exists, such as in the cases of lymphoma, an exploratory laparotomy for tissue diagnosis remains justified.

When acute pancreatitis develops in a patient with primary nonpancreatic malignancy, conservative measures such as nasogastric tube suction, intravenous fluids, and the use of analgesics may be used first, and occasionally the pancreatitis may subside in a few days.[8,15,17] If clinical pancreatitis persists and a histologic diagnosis of pancreatic metastases has been made, systemic chemotherapy or abdominal irradiation should be considered in patients with small-cell carcinoma or lymphoma. Yeung and colleagues reported the cases of three patients with metastasis-induced acute pancreatitis associated with small-cell lung cancer, and clinical pancreatitis resolved completely two days, one week, and four weeks, respectively, after combination chemotherapy was instituted.[7] Levine and Danovitch reported the case of a patient with bronchogenic carcinoma-induced pancreatitis that did not respond to abdominal irradiation, whereas abdominal irradiation provided palliation in one of our patients with lymphoma (patient 5).

Acute pancreatitis due to metastasis seems to be an ominous prognostic sign in patients with primary nonpancreatic malignancy. Among those patients with survival data documented,[6-13,16,17,21,22] the vast majority died within six months after the diagnosis of acute pancreatitis. Only two patients with non-Hodgkin's lymphoma survived for more than six months.[16,17]

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Spontaneous Intracranial Hypotension

An Uncommon and Underrecognized Cause of Headache

MICHAEL B. JACOBS, MD
PHILIP H. WASSERSTEIN, MD
Stanford, California

ALTHOUGH WELL DESCRIBED in the neurologic literature,[1-3] spontaneous intracranial hypotension (also called primary intracranial hypotension, primary cerebrospinal fluid hypotension, spontaneous hypoliquorrhea, and a number of other names) is generally not mentioned in reviews of headache diagnosis and treatment in the internal medicine literature.[4-6] We report a case of this headache disorder and review its characteristics, pathogenesis, and treatment.

Report of a Case

The patient, a 25-year-old woman with an unremarkable medical history, suddenly had moderate occipital and posterior cervical discomfort. She felt nauseated, vomited, and took a nap. On rising she had severe cervico-occipital pain—"the worst I ever felt in my life"—whenever she tried to sit or stand. When she lay down, she felt perfectly well, but she was essentially unable to stand or sit.

There was no history of fever or head trauma. The results of a general physical examination and the neurologic examination were within normal limits. A complete blood count with differential leukocyte count was normal. Magnetic resonance imaging (MRI) of the head showed the tips of the cerebellar tonsils to be within the foramen magnum.

A lumbar puncture was done with the patient in the lateral decubitus position. The opening pressure was 20 mm of cerebrospinal fluid (CSF). The CSF flowed from the needle slowly, but the flow rate increased with a Valsalva maneuver. The fluid was acellular, and protein and glucose concentrations were normal. No imaging study was done to look for an extradural CSF leak.

Treatment included a five-day course of corticosteroids, a high-salt diet, salt tablet supplements, and extra oral fluids. The headache was decreased at two weeks and gone in eight weeks.

Discussion

Headache is an extremely common outpatient problem with an extensive differential diagnosis. Most headaches, particularly in young people, are not the result of intracranial disease but are considered to represent tension or vascular headache, particularly if the headaches are chronic. The most common vascular headache is the common migraine; less common types include classic migraine, cluster headache, cough headache, exertional headache, and coitus-associated headache. New-onset and acute headaches raise

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From the Departments of Medicine (Dr Jacobs) and Neurology (Dr Wasserstein), Stanford University Medical Center, Stanford, California.

Reprint requests to Michael B. Jacobs, MD, Department of Medicine, Stanford University Medical Center, Stanford, CA 94305-5235.

ABBREVIATIONS USED IN TEXT

CSF = cerebrospinal fluid
MRI = magnetic resonance imaging

concern about the possibility of some serious intracranial disorder. Possibilities include infection (meningitis, encephalitis, or brain abscess), hemorrhage (subdural, subarachnoid, or intracerebral), and tumor (benign primary brain tumor, malignant primary brain tumor, or metastatic tumor).

Spontaneous intracranial hypotension is a type of new-onset headache with one essential clinical feature: prompt and striking relief of pain when the patient lies down, with prompt recurrence of pain on sitting or standing. This aspect of the headache is identical to that of the readily recognized post-lumbar puncture headache, but there has been no preceding lumbar puncture. A definitive diagnosis requires the demonstration of a low opening pressure when a lumbar puncture is done: the pressure should be less than 70 mm of CSF, perhaps less than 30 mm of CSF if the strictest diagnostic criterion is followed. The spinal fluid should flow freely with a Valsalva maneuver to confirm that the pressure reading accurately reflects intracranial pressure; if it does not, there may be a spinal block or the needle may be improperly placed. Sometimes there may actually be a negative opening pressure: a sucking sound can be heard when the stylet is withdrawn from the needle, and imaging studies may then show air in the subarachnoid space.

The headache is characteristically bilateral and variably posterior, holocranial, or anterior. Associated symptoms may include vertigo, nausea, vomiting, blurred vision, photophobia, neck stiffness, and occipitocervical pain with neck flexion. Confusion raises the question of bilateral subdural hematomas (sometimes occurring in this condition), whereas focal neurologic findings or seizures are rarely enough reported in this condition that other diagnoses should be considered.

Cerebrospinal fluid is often normal, but there may be increased protein (usually less than 1 gram per liter [100 mg per dl]) or an abnormal number of cells (particularly erythrocytes but sometimes leukocytes). The increased number of erythrocytes in the CSF could result from a number of causes: postulated hyperemia of the brain and meninges with diapedesis of erythrocytes into the CSF, mechanical disruption of bridging cortical veins by traction, and unrecognized traumatic lumbar puncture (particularly likely to occur in a patient with slow or no CSF flow from the needle.[1,2]

Brain imaging studies are usually normal; however, some patients may show bilateral subdural hematomas, caudal displacement of the cerebellar hemispheres and brain stem, or decreased size of the ventricles and basal cisterns. Subdural hematomas are thought to develop as the result of low CSF pressure rather than vice versa; traction on bridging cortical veins (because of a lack of buoyant support of the brain by the CSF) would be the most likely mechanism.

Bell and co-workers classified the intracranial hypotension syndromes into five types: primary or spontaneous, post-lumbar puncture, following head injury, following craniotomy, and as a result of severe intravascular volume depletion.[1] The spontaneous type and that following a craniotomy probably result from CSF leakage through a dural tear. The last type, severe intravascular volume depletion, could result from either decreased intracranial volume in the vascular compartment or decreased production of CSF by the choroid plexus.

The cause of the decreased intracranial pressure in the spontaneous syndrome is unknown, but there are three main hypotheses: hyposecretion, hyperabsorption, or leakage through a dural tear. Schaltenbrand (who first characterized this headache in 1938) considered it most likely that the decreased intracranial pressure was the result of a decreased rate of secretion of CSF by the choroid plexus.[7] Perhaps the strongest argument in favor of this hypothesis is the persistent CSF xanthochromia noted in some cases.[2] Isotope cisternography has provided some evidence to support the hypothesis of hyperabsorption,[3,8] but sometimes the clinical history,[9,10] clinical findings,[10] or radionuclide imaging[11] strongly support the concept of an extradural CSF leak. No one theory explains every feature of each case, and most likely this is a syndrome with a number of causes.

The mechanism of headache in intracranial hypotension is uncertain. Traction on pain-generating intracranial structures due to a lack of the buoyant effect of CSF on the brain has generally been postulated. Low intracranial pressure and CSF leaks do not always lead to the development of orthostatic headaches, however. When Marshall repeated lumbar punctures at 24 hours, CSF pressures of less than 60 mm occurred in 3 of 5 patients with positional headache and in 7 of 37 without headache ($P = .078$).[12] Clearly headache develops in some patients with low intracranial pressure and not in others, but the cause for this variability is unknown.

This patient had cerebellar tonsils that protruded into the foramen magnum, suggesting a Chiari I malformation. This malformation may present during adult life with a variety of symptoms including headache, diplopia, syncope, quadriparesis, or sensory abnormalities from associated syringomyelia. Low-lying cerebellar tonsils are being detected much more frequently now that head MRIs are commonly done, and it is probable that this patient's MRI findings were entirely coincidental. The possibility can be considered that her occipital headache developed from intracranial hypotension because of her low-lying cerebellar tonsils.

Most treatments have had as their rationale restoring normal CSF volume or eliminating a presumed CSF leak; without more definite knowledge of the pathogenesis of the syndrome, however, treatments may be regarded as empiric. Treatment efficacy is difficult to evaluate because the condition is self-limited and therapeutic regimens uncontrolled; there are reports of dramatic improvement with a variety of treatments. The simplest "treatment" is the avoidance of the upright position plus time. Systemic treatments postulated to help restore normal CSF volume have included inhalation of 5% carbon dioxide, increased oral fluid and salt intake, corticosteroid use,[2,13] and the intravenous administration of a normal saline solution. Intravenous caffeine and oral theophylline have been used primarily for post-lumbar puncture headache,[14,15] but the attempt has been made to use oral caffeine for the spontaneous syndrome.[3] Headaches have been relieved after single intrathecal injections of saline solution[2,16] and after continuous epidural saline infusions.[11,17] Epidural saline solution and epidural autologous blood "patching" have been postulated to eliminate extradural leakage of CSF, but Raskin has proposed that such therapy might be effective because of an indirect inactivation of adenosine receptors on cerebral blood vessels.[15] Epidural

autologous blood has been used primarily in patients with persistent post-lumbar puncture headache, but similar benefit has been noted in patients with spontaneous intracranial hypotension.[18,19]

Spontaneous intracranial hypotension needs to be considered when a patient presents with a new onset of headaches. In the absence of known causes of intracranial hypotension, the diagnosis is suggested by orthostatic headache and confirmed by lumbar puncture. This condition is generally benign and self-limited, but some patients require treatment of associated subdural hematoma or of persistent headache. Therapeutic modalities used have included increased oral fluid and salt intake, corticosteroids, caffeine, theophylline, intrathecal saline, epidural saline, and the use of autologous epidural blood "patching."

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Radiologic Case

Lung Mass and Hemoptysis in a Patient With Tuberculosis

KRISHNAN PADMANABHAN, MD; SANTI R. DHAR, MD; *and* KIAT YEO, MD, *Brooklyn, New York*

A "Radiologic Case" is published in this format on a regular basis. Physicians interested in contributing to the series are encouraged to send their radiologic cases to the series' editor.

JONATHAN M. LEVY, MD
Assistant Editor

A 59-year-old Chinese man was admitted to the hospital with massive hemoptysis. He had a history of cavitary pulmonary tuberculosis, with episodes of mild hemoptysis over the past two years. A chest x-ray film and computed tomographic (CT) scan of the chest were done (Figures 1 and 2).

What are the findings?

What is the most likely diagnosis?

What is the prognosis?

SEE FOLLOWING PAGE FOR DIAGNOSIS AND DISCUSSION

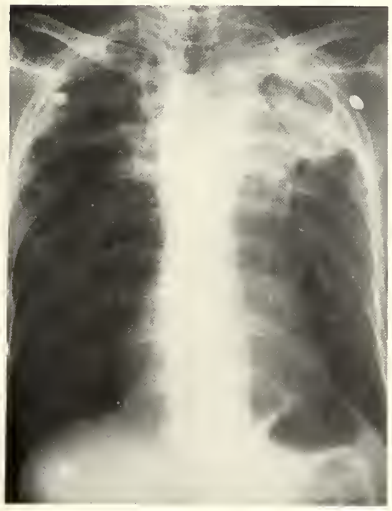

Figure 1.—A posteroanterior chest film shows a cavity in the left upper lobe with an intracavitary mass.

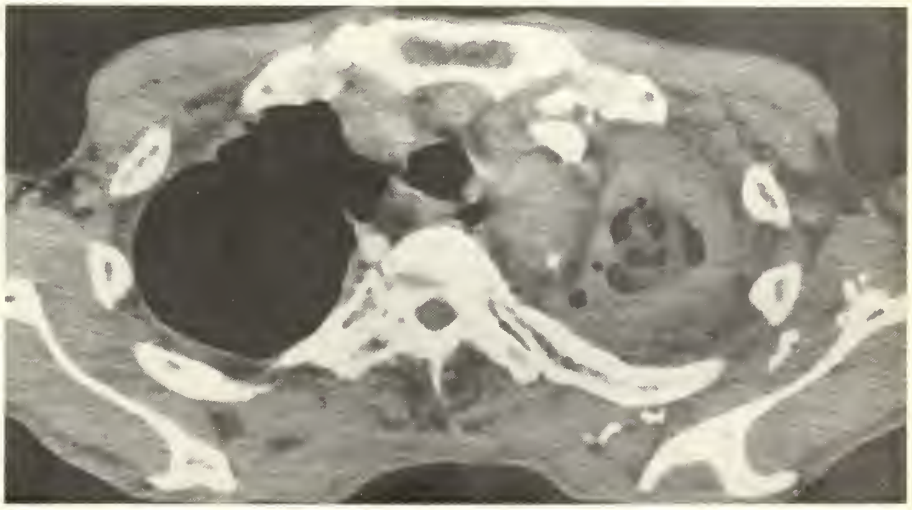

Figure 2.—A computed tomographic scan of the pulmonary apices shows multiple cavities within the mass in the left apex.

(Padmanabhan K, Dhar SR, Yeo K: Lung mass and hemoptysis in a patient with tuberculosis. West J Med 1991 Aug; 155:181-182)

From the Department of Pulmonary Medicine, Coney Island Hospital, Brooklyn, New York (Drs Padmanabhan, Dhar, and Yeo), and the Department of Medicine, State University of New York, Health Science Center at Brooklyn, College of Medicine (Drs Padmanabhan and Dhar).

Reprint requests to Krishnan Padmanabhan, MD, Department of Pulmonary Medicine, Coney Island Hospital, 2601 Ocean Parkway, Brooklyn, NY, 11235.

ANSWER: Fungus ball (intracavitary mass due to pulmonary aspergilloma)

THE CHEST FILM (Figure 1) shows a cavity in the left upper lobe with an irregular outer wall. There is an intracavitary mass, which has an incomplete rim of air separating it from the cavity wall. This represents the "crescent" or "ball and halo" sign, which is characteristic of pulmonary aspergilloma. The CT scan (Figure 2) also shows the thick-walled cavity, which contains a mass that is studded with multiple areas of lucency, giving it a sponge-like appearance. This has been described as a characteristic of pulmonary aspergilloma on CT.

Aspergillus mycetomas (fungus balls) are matted masses of fungal hyphae due to saprophytic colonization in areas of lung destroyed as a result of tuberculosis, sarcoidosis, histoplasmosis, emphysema, necrotizing pneumonia, bronchiectasis, pulmonary infarct, or cavitating neoplasm. Symptoms are generally those of the underlying disease. Hemoptysis is the most common complication, occurring in 55% to 85% of cases. The natural course is variable and is dictated by the severity of the underlying disease and the presence or absence of massive hemoptysis. A five-year mortality rate of 31% has been reported.

The diagnosis of pulmonary aspergilloma is usually made radiographically and by identifying the presence of precipitin titers to aspergillus antigen in the blood. Sputum specimens often grow the fungus, but this is not essential for the diagnosis. A CT scan of the chest can provide further confirmation of the diagnosis based on characteristic findings. These include the classic mobile intracavitary mass partially surrounded by air; an irregular, fixed, sponge-like density within the cavity (as in our patient); and, in the early stage, the presence of intersecting fungal fronds arising from the cavity wall and forming an intracavitary network. Computed tomographic scans of the chest can often help to make the diagnosis earlier, especially when the chest film appearance is not typical. They can also help to better identify the number and site of lesions.

Management strategies for aspergilloma depend on the adequacy of lung function and reserve. They include supportive therapy, the intracavitary instillation of amphotericin B, and lung resection and bronchial artery embolization in cases of significant hemoptysis. Our patient had an emergency resection of the left lung because of the life-threatening hemoptysis. The lung specimen revealed an intracavitary mass composed of mycelial hyphae of the *Aspergillus* species in a matrix of mucin, fibrin, and inflammatory exudate. No involvement of adjacent lung tissue was noted.

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Commentary

The Perils of Providing Medical Opinion
A State Medical Association's Experience

HIBBARD E. WILLIAMS, MD, *Davis*, and LINDA L. RAMSEY, *San Francisco, California*

After nearly 20 years, the California Medical Association (CMA) is reconsidering its responsibility to provide opinions on questions of clinical medical practice. Lawsuits prompted this reconsideration. We describe the CMA's experience with a medical practice opinion program and the benefits and risks to a professional association of participating in the assessment of technology.

Background

The California Medical Association has an active tradition of involvement in scientific and educational affairs. Its 1856 charter gives the association's purpose: "To promote the science and art of medicine; the care and well-being of patients; the protection of the public health and the betterment of the medical profession." The creation of the CMA's Scientific Board in 1963 gave these activities added emphasis.

The board is a forum of chairs of the association's 24 scientific advisory panels, groups formed as a specialty-based resource to plan educational activities, prepare the Epitomes section of THE WESTERN JOURNAL OF MEDICINE, and provide scientific opinion to CMA, its component societies, and the public.

The advisory panels reflect both a geographic mix and a balance between academic physicians and those in private practice. Each advisory panel has about 16 members, including a chair or senior representative of the appropriate specialty department of the eight California medical schools; the principal officers of the major statewide specialty societies; and several other members with distinguished scientific or educational credentials elected to represent privately practicing physicians in the specialty.

In the early 1970s, the California Medical Association began receiving an increasing number of requests for opinions on medical practice issues. The questions came from newly formed medical care foundations, health insurance carriers, the State Department of Health Services' Medicaid program, the Medical Board of California (then known as the Board of Medical Quality Assurance), hospital medical staffs, and from various individuals. Most of the inquirers wanted to know whether a particular medical procedure, technique, or device was accepted medical practice. Underlying many of the questions was a payer's need to make a reimbursement decision. But concerns about hospital medical staff privileges, county medical society membership, and medical board investigations triggered questions as well. All of these groups were seeking an authoritative source for opinions that were likely to have far-reaching effects.

As a result of these requests for medical opinions and the commitment of the CMA to promote the science and art of medicine, the medical practice opinion program was initiated in 1974.

The Medical Practice Opinion Program

The CMA Medical Practice Opinion Program selectively accepted requests to review emerging, new, and, to a lesser extent, established medical and surgical practices, procedures, and medical care devices for their safety, effectiveness, limitations, and general level of acceptance in the medical community.

The program never considered cost and benefit questions or insurance coverage issues. The opinions given were based on the personal knowledge and experience of the specialists who served on the scientific advisory panels and consultants selected by the panel members. The opinions addressed broad issues—not medical care given in a specific case.

Persons or organizations seeking CMA review of a medical practice question submitted a written request explaining the reason for the question and providing sufficient background to describe the issue. The request then was sent to the chairs of the 24 scientific advisory panels to determine whether to accept the question and, if so, which specialties should contribute to an answer.

Once accepted, the question was circulated to members of the appropriate advisory panels with relevant articles from peer-reviewed journals, review reports from authoritative organizations such as the National Institutes of Health, policy statements from national specialty societies, and other information from recognized experts in the field. All of the panel comments received were distilled into a summary opinion that was reviewed by the panel chair(s); returned to the individual respondents for ratification; and presented to the CMA Commission on Quality Care Review, a multispecialty oversight body, for final approval.

Unanimity was sought on all medical practice opinions, but when agreement could not be reached, an opinion was drafted to reflect the broadest common ground among the respondents, with the points of difference stated clearly, without bias or attribution to specific specialties or persons. The individual comments of the advisory panel members remained confidential throughout this process. There was a review mechanism to assure that all opinions in circula-

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From the Scientific Board (Dr Williams) and Division of Scientific and Educational Activities (Ms Ramsey), California Medical Association, San Francisco, and the University of California, Davis, School of Medicine (Dr Williams).

Reprint requests to Linda L. Ramsey, Director, Division of Scientific and Educational Activities, California Medical Association, PO Box 7690, San Francisco, CA 94120-7690.

tion remained current or were dropped. The final opinion was shared with the original inquirer and published in this journal.

During the first 15 years of its existence, the Medical Practice Opinion Program grew in volume and sophistication. The opinion formulation process became more formal. Guidelines for administering the program were developed and approved by the governing council of the CMA in 1975 and were periodically reviewed and revised. While the CMA never solicited inquiries to the program, the number of questions steadily increased. During the years 1972 to 1987, nearly 350 opinions were issued.

Legal Problems Surface

The first lawsuit generated by a medical practice opinion was filed in 1982 and involved a physician's challenge to an opinion concerning the surgical procedure, bilateral carotid body resection. The opinion was a consensus of 46 panel members from chest diseases, internal medicine, and general surgery and stated that the procedure was not accepted medical practice. The physician plaintiff maintained that the procedure was accepted practice and that he had suffered substantial economic loss as a result of the opinion and was entitled to compensation under federal antitrust laws.

Most insurance carriers denied coverage for bilateral carotid body resection (Blue Shield was later added as a defendant in the lawsuit), and in 1980 the Joint Commission on Accreditation of Hospitals warned the hospital where the plaintiff practiced that allowing unacceptable surgical procedures such as bilateral carotid body resection could jeopardize the hospital's accreditation. These events, it was alleged, flowed from the issuance of the medical practice opinion.

Judicial proceedings extended over six years and ultimately resulted in a judgment in favor of the CMA. In dismissing the case, the judge noted that "the conduct . . . is entirely consistent with organizations and professions acting in good faith to fulfill their legal and professional responsibilities." The Association's defense costs in this suit, covered by the CMA's liability insurance carrier, were estimated to be $250,000.

A second lawsuit, filed in 1988, also was a complaint for damages under federal antitrust laws. The plaintiff was a laboratory that did cytotoxic testing for food allergy and advised its clients on the basis of test results to avoid certain foods and substances and to substitute others. The trigger for the suit was a CMA medical practice opinion stating that cytotoxic testing was not accepted medical practice. The plaintiff claimed that this opinion was part of a conspiracy by the allergy and medical associations to suppress a nontraditional method of allergy testing so that the incomes of "traditional" allergists would be protected from competition.

In an action preceding the lawsuit, the Laboratory Field Services Section of the State Department of Health Services decided to regulate laboratories engaged in cytotoxic testing as other clinical laboratories were regulated. Regulation by the State Department of Health Services entailed mandatory proficiency testing, which the cytotoxic testing laboratories resisted. Laboratories offering cytotoxic testing maintained that they were not engaged in the practice of medicine but offered only nutritional counseling. To bring these laboratories under state regulation, it was necessary to establish that they were purporting to diagnose or treat disease.

The Medical Board of California opined that the cytotoxic test was being used to diagnose food allergy. That determination allowed the State Department of Health Services to impose proficiency testing requirements on cytotoxic laboratories. The combination of declining insurance reimbursement for cytotoxic testing and the imposition of proficiency testing regulations created the economic hardship that the plaintiffs in this second lawsuit attributed to the medical practice opinion issued by the CMA.

This action also was resolved in the CMA's favor in 1990 at a relatively early stage of the proceeding but cost the CMA $50,000—the amount of the deductible copayment in the association's liability insurance policy. Additional legal expenses incurred by all plaintiffs meant that well over a quarter of a million dollars was spent to have this case dismissed.

Program Changes in Response to Legal Concerns

After the second lawsuit was filed in 1988, legal counsel recommended that the CMA impose an immediate moratorium on medical practice opinions until the risks of the program could be assessed. The only medical practice questions accepted after 1988 were those generated by governmental entities such as insurance companies serving as claims intermediaries for the Medicare program in California. Responses to agents of government were considered protected by the Noerr-Pennington doctrine, which is based on the constitutional rights to freedom of speech and to petition the government. Other inquiries were referred to other sources for scientific information.

Pros and Cons of Medical Practice Opinion Programs

Medical practice guidelines are intended to protect patients from unproven, unsafe, and inappropriate procedures. Insurance firms rely on such guidelines to make rational reimbursement decisions. By generating medical practice opinions, physician organizations help assure that reimbursement patterns reflect community standards and that resources are neither wasted on outmoded technologies nor inappropriately denied for needed care. Such opinions become increasingly valuable as governmental battles are waged for scarce health care dollars and medical groups and others seek to expand health insurance coverage to uninsured populations. Moreover, organized medicine's willingness to accept some liability risk in pursuit of patient protection contributes to the image of the medical profession as socially responsible and dedicated to the public good.

The legal defense costs of challenged opinions are potentially devastating, however. The costs associated with defending an antitrust lawsuit can easily consume a substantial part of a medical association's financial resources, even if the suit has no basis. Because of the potential for lengthy court proceedings and punitive awards of treble damages, association liability insurance providing coverage for antitrust actions can be prohibitively expensive—if available at all.

Just as physicians may practice defensive medicine to avoid lawsuits, medical associations are pressured to buttress activities such as the Medical Practice Opinion Program with attorney-recommended safeguards to reduce legal liability exposure. The consequence may be a program increasingly ponderous, cautious, and unresponsive to the needs of its constituency.

Risk reduction strategies implemented by other associations range from elaborate disclosure of interest statements

by each respondent to the suppression of negative opinions and the issuance of positive opinions only.

Interestingly, the physicians providing opinions to the CMA were among the strongest supporters of the program—despite their risk of becoming embroiled in legal wrangles over contested opinions. No physician expressed reluctance to participate, and those who were deposed on the two lawsuits discussed earlier were willing witnesses to the value of the Medical Practice Opinion Program. All 24 of the Scientific Board's advisory panels have voted repeatedly to support the program and to petition the CMA Board of Trustees for an end to the moratorium on the issuance of scientific opinions. Some physicians expressed resentment that this type of program may become another casualty of needless intrusion and interference by the American legal system. The Advisory Panel on Neurosurgery recommended in 1990: "If the medical practice opinion program is discontinued or modified, the CMA should use all means available to inform its membership and the general public why it cannot respond to questions on medical practice."

The CMA adopted a cautious approach. In 1989 its Board of Trustees voted to continue the moratorium indefinitely while exploring options such as liability exemption legislation and other means to reduce liability risk to a level deemed acceptable before reactivating the program.

Possible Solutions

The goal of the CMA is to continue the Medical Practice Opinion Program if the risk of legal liability can be reduced to an acceptable level. These are the solutions that are now being assessed:

- Eliminate the Medical Practice Opinion Program.

This option has the appeal of saving the medical association from the future risk of lawsuits arising from program opinions. On the negative side, it is clear that determinations of acceptable medical practice will be made—if not by organized medicine, then by others. If physicians abrogate their role as arbiters of quality-care decisions, these decisions are likely to be made by people for whom good patient care and honest science are not the highest priority.

- Continue the Medical Practice Opinion Program but respond only to requests from governmental entities.

While this option provides the CMA with a limited sense of security based on the applicability of the Noerr-Pennington doctrine, it severely limits the number of questions that can be accepted. Our data suggest that at the very least, more than 80% of questions would be eliminated—probably more as the program's visibility diminished.

- Direct all requests for medical opinion through the Medical Board of California.

This option would require an agreement, adopted through the agency regulatory process, that the state medical board receive all questions, refer them to the CMA or other medical associations for comment, and serve as the repository of final opinions. The Medical Board of California seems willing to consider this approach, based on its perception of the value of a state-based medical assessment program. To obtain the benefits of legal immunity that medical board oversight would provide, however, the board must, by law, engage in active supervision of the program on whose opinions it relies. This degree of supervision over a CMA program by a state agency could be unacceptable to the CMA. It could require more resources than the board wishes to devote to the enterprise. The potential for political influence in such an arrangement also is a concern.

- Seek immunity for this and similar opinion programs through legislative action.

This approach would require enacting legislation containing a statement that clearly expresses the California legislature's intention to replace competition with regulation for the purpose of ensuring the provision of effective and efficient health care to Californians; and the creation of an actively supervised program to assist in the dissemination of medical information necessary to the state's health, safety, and welfare. The new entity would be a Committee on Health Care Technology that would provide a framework for the advance notice of opinions under consideration, referral of issues to groups such as the CMA that meet an established standard, and procedures for due process and the appeal of adverse decisions. If enacted, such a law could allow the CMA and other professional associations to provide scientific opinion freely, without fear of unreasonable legal risk. The disadvantages of this option include the difficulty in enacting such legislation over predictable objections from trial attorney groups and the potential political influences that state control of the program could bring.

- Reactivate the Medical Practice Opinion Program and resume full activity.

Adopting this action would require the recognition that the costs of the program, including legal defense costs, are reasonable given the value of the program to the profession and to patients.

Conclusion

Failure to reactivate the Medical Practice Opinion Program allows a program designed for the protection of patients and the greater public good to be destroyed by intimidation. Medical associations must endeavor to prevent persons from using the legal system to protect practice methods that have been judged unacceptable. Although we cannot envision a risk-free world, medical associations must accept their responsibility to discourage such suits by a strong defense.

Society needs the assistance of all qualified professional associations to evaluate the effectiveness of medical care. The medical profession needs reasonable professional autonomy in expressing scientific opinion. Most important, patients need programs such as the Medical Practice Opinion Program.

Commentary

Medical Education, Training, and Health Care Services in the Republic of Singapore

CHIN HIN CHEW, MD, FACP, FRCP, FRACP, *Republic of Singapore*

Singapore is an independent island city-state situated in Southeast Asia just 1 degree north of the equator. It has a land area of only 625 km^2 and a population of 2.75 million. Despite its relatively high population density and tropical location where epidemics still prevail, Singapore has a remarkable health record and freedom from the major infectious diseases. The city is clean, and more than 85% of the population lives in high-rise public housing apartments. The per capita income is US$9,000 a year. The infant mortality rate of 7 per 1,000 live births and life expectancy of 74 years compare favorably with the rest of the world.[1,2]

Medical Education and Training

The record of health services in Singapore is an account of the acceptance of Western medicine by the multiracial community. The founding in 1905 of the King Edward VII College of Medicine was a milestone in Singapore's medical history.[3,4] This college was the predecessor of the Faculty of Medicine of the National University of Singapore, which now graduates about 200 physicians annually. There are 3,400 physicians in Singapore,[5] a physician-to-population ratio of 1:800.

The medical undergraduate curriculum comprises five years of study and corresponds closely to that of the United Kingdom. The criteria for admission to the medical school are stringent and include top-level passes of the Singapore-Cambridge general certificate in advanced level examination in chemistry, zoology (or botany, biology), and physics, plus a successful interview. The clinical course of three years emphasizes practical bedside teaching of medicine, pediatrics, surgery, orthopedic surgery, and obstetrics and gynecology. To practice medicine in Singapore, graduates must complete a year of supervised training as an intern in hospitals recognized for this purpose. They may then seek registration as fully qualified medical practitioners with the Singapore Medical Council.

Postgraduate Medical Education and Training

Medical education is a lifelong process. All new graduates following their internship work in the medical service of the government or university for at least five years. After the first year of service, they are eligible to embark on formal training either as a specialist or in general family practice. The first period of training is three years. After successful higher professional examinations in specialties or general practice, candidates are given further opportunities for structured training in their respective disciplines for three to four more years. Thereafter they may apply for certification as a specialist and for membership in the Academy of Medicine. They are also eligible for registration as a specialist with the Singapore Medical Council.[5] More than 30 disciplines are included in this certification process. Specialist certification is the joint responsibility of the Academy of Medicine and the School of Postgraduate Medical Studies.

The Academy of Medicine, the College of General Practitioners, and the School of Postgraduate Medical Studies

The School of Postgraduate Medical Studies is administered by a board comprising representatives from the Faculty of Medicine of the National University of Singapore, the Academy of Medicine, and the Ministry of Health. The school administers the Master of Medicine examinations, which correspond to membership or fellowship examinations of the United Kingdom or Australasian Royal Colleges. To ensure that high and corresponding standards of examinations are maintained, external examiners from the Royal Colleges are appointed.[6] Since the establishment of the school in 1970, more than 800 physicians have successfully completed these higher examinations.

The Academy of Medicine, which was founded in 1957, is the professional corporate body for medical and dental specialists in Singapore. The Academy is patterned on the Royal Colleges in the United Kingdom and Australasia, but unlike these colleges, which are responsible for individual disciplines, this body embraces all specialties. Thus, the Academy includes all specialists and consultants in Singapore—the government service, the university, and the private sector. Its main missions are advancing the art and science of medicine, maintaining the highest standards of professional and ethical practice, and improving postgraduate education and training. Membership requirements are stringent and include a waiting period of at least eight years after graduation and at least five years of recognized experience in a specialty, three years of which must be after obtaining an approved postgraduate degree.[4,7]

The College of General Practitioners was founded in 1971 as the professional corporate body for practitioners of family medicine in Singapore. It works closely with the Ministry of Health and the Department of Community, Occupational, and Family Medicine of the National University of Singapore and conducts examinations for membership. Phy-

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From the Academy of Medicine, Republic of Singapore.
Reprint requests to Chin Hin Chew, MD, FACP, FRCP, FRACP, 15 Akyab Rd, Singapore 1130, Republic of Singapore.

sicians who choose family practice as their career are encouraged to take this examination and to uphold the high standards of general practice in Singapore.[8]

Continuing Medical Education

Continuing medical education programs in Singapore include lectures, seminars, conferences, scientific meetings, and formal postgraduate courses organized by the main professional bodies and the many related specialist societies and organizations. Singapore also is a choice venue for international and regional congresses and conferences. The most recent, the 26th International Congress of Ophthalmology, attracted 10,000 participants. In addition, the College of General Practitioners and the Singapore Medical Association hold annual scientific meetings. The Academy of Medicine organizes an annual joint Singapore-Malaysia Congress of Medicine with its sister body in Malaysia, which regularly attracts international participation.[4]

Singapore has a formal voluntary continuing medical education program resembling that of the Accreditation Council for Continuing Medical Education of the United States.[9] Physicians are also encouraged to keep abreast of advances through articles in medical journals. The two principal medical journals of Singapore are the *Annals of the Academy of Medicine* and the *Singapore Medical Journal*, both of which are internationally recognized.[9]

Health Care Services

The pattern of disease conditions in Singapore has changed over the years with improvements in the standard of living and health services. Before and immediately after World War II, the main causes of death were infectious diseases such as tuberculosis and dysentery. Today cancer, heart disease, and strokes account for more than 50% of all deaths in Singapore. The most common heart condition is ischemic heart disease, whereas the commonest types of cancer are lung, colorectal, stomach, and liver.[1]

With the rapid growth in Singapore's population after World War II, a family planning and population board was established in 1966 to undertake population control. The need for Singaporeans to plan for a "two-child family" was intensively publicized. By 1975 Singapore had attained replacement level fertility, and the total fertility rate dropped to 2.07 per woman from 6.41 in 1957. This rate continued to decline alarmingly and reached an all-time low of 1.44 in 1986. New measures had to be undertaken, and a comprehensive package of generous incentives to promote a "three-child family" was introduced in 1987 to replace the population at a reasonable rate. For 1989, the rate rose to 1.93. The trend is being closely monitored.

The Ministry of Health has the overall responsibility for Singapore's health policies and administers the government health services through the Hospital, Primary Health, and Dental Divisions, supported by other paramedical and ancillary services. It works closely with the Ministry of the Environment in maintaining good environmental hygiene and control of communicable diseases and with the Ministry of Labour in monitoring industrial and occupational diseases.[2]

Singapore has a dual system of health care services—a public assistance system administered by the government and a private system available in private clinics and hospitals. The public has the choice of seeking medical care and services in the public or private sectors. Government health services are heavily subsidized to ensure that health care is available to all Singaporeans.

Singapore's health care philosophy is to build a healthy community through a vigorous preventive health care program. Singaporeans are taught to be responsible for their own health and are informed of the adverse consequences of smoking, bad diet, and sedentary life-styles. Singaporeans are educated on stress-related problems and on the counseling services that are readily available in government and private centers. Close monitoring of these problems is undertaken, especially as Singapore becomes an urban and increasingly affluent society. We have an efficient and effective childhood immunization program against diseases such as tuberculosis, poliomyelitis, diphtheria, whooping cough, measles, mumps, rubella, and hepatitis B. Coverage is excellent and has led to the eradication of such life-threatening infections as poliomyelitis, diphtheria, and miliary tuberculosis.[1,2]

Singaporeans are encouraged to build up their financial resources to meet their future health care requirements. This is achieved through a compulsory governmental savings scheme known as Medisave, with monthly contributions provided equally both by the worker and the employer. This amounts to 6% of a person's salary. The scheme allows those covered the ability to pay for their health care needs and those of their immediate family.[10] This is supplemented by a voluntary governmental catastrophic illness insurance, Medishield, to cover medical expenses arising from major and prolonged illnesses.[11]

As with other countries, Singapore's expenditure on health care has been rising; in 1988 the total expenditure of the Ministry of Health was approximately US$280 million, or about US$95 per capita. Most of this is spent on hospital services. The total national health expenditure for both the government and private sectors constitutes about 3% of the country's gross domestic product. Medical treatment is highly subsidized by government, being about 70% subsidized in 1988.[1]

The government sector provides approximately 80% of hospital services and 30% of primary health care, and the private sector provides the balance.

Hospital services are provided through nine government-administered hospitals with about 8,000 beds and 11 private hospitals with about 1,800 beds.[1] Specialized disciplines such as cardiovascular and thoracic surgery and cardiology, neurosurgery and neurology, and plastic and reconstructive surgery are provided in three large government hospitals. Nephrology and dialysis centers, geriatric medicine, assisted reproduction, and in vitro fertilization are also available in some of these hospitals and a couple of private hospitals.

Primary health care services of the Ministry of Health are provided through a network of polyclinics.[1] The services are comprehensive and include primary general medical treatment, maternal and child health care, home nursing, day care for the elderly, and health education and counseling. Children in schools receive free medical and dental services that include periodic screening, immunization, health education, and treatment. Most curative primary health care services are provided by family physicians or general practitioners in privately owned clinics. There are in addition a number of traditional Chinese herbalists who provide basic treatment. They are not officially recognized, however, and are not permitted to prescribe drugs.

Medical Professionals

Singapore has 3,400 physicians, 600 dental surgeons, 560 pharmacists, and more than 9,600 nurses and midwives. These professionals must be registered with their respective statutory bodies—the Singapore Medical Council, the Dental Board, the Pharmacy Board, and the Singapore Nursing Board—before they are allowed to practice in Singapore. These bodies are also responsible for maintaining standards and regulating professional and ethical conduct.[2]

Medical Research

Extensive medical research is carried out at government or university institutions. The recent establishment of the Institute of Molecular and Cell Biology of the National University of Singapore and the Department of Clinical Research of the Ministry of Health at the Singapore General Hospital has provided a tremendous impetus to medical research, with facilities available for applied and basic medical research. In addition, collaborative projects have been undertaken with international bodies such as the World Health Organization and the British Medical Research Council.[12]

Priorities for research have been based on prevailing conditions and problems. Thus, in the late 1950s, research on the immunization of poliomyelitis led to the comprehensive administration of oral Sabin vaccine and eradication of the disease.[13] Results of collaborative studies with the British Medical Research Council on antituberculous chemotherapy regimens since the 1960s led to the universal acceptance of these regimens in routine practice, particularly with regard to supervised and short-course chemotherapy.[14-20] Other examples are the ready adoption of hepatitis B immunization, the widespread use of bacille Calmette-Guérin vaccine in developing countries,[21] and the eradication of diphtheria. Some other areas of intense research activities include reproductive endocrinology, population control measures, industrial dermatology, sexually transmitted diseases, oncology with particular reference to cause and treatment, immunology, and numerous therapeutic trials.

Epidemiologic studies have also been carried out. The recent problem of sudden unexpected nocturnal deaths of young Thai workers in Singapore has been documented.[22] This is not peculiar to only those in Singapore; it is known to occur also in northeast Thailand. The exact cause is unknown, but it is likely to be multifactorial. Most of these research studies have been or will be published in reputable journals or presented at international conferences.

Conclusion

Singapore celebrated its 25th anniversary as an independent republic last year. With virtually no natural resources, its path to statehood, nationhood, and sovereignty has not been easy. Indeed, many thought the country's survival as an independent nation unlikely. Nevertheless, with a strong and pragmatic government led by a remarkable generation of ministers and supported by a highly motivated and disciplined people, Singapore has not only survived but has forged ahead through rapid industrialization and hard work. It has emerged as a modern metropolis on the verge of joining the ranks of the world's developed countries. With an efficient infrastructure, Singapore has achieved an enviable reputation as a major business center in the global marketplace. Similarly in the medical fields, Singaporeans can be confident that their health care status and medical facilities will continue to improve, with the rapid advances and breakthroughs in preventive medicine, medical science, and technology and the assurance of continuing support by the government.

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Editorials

Understanding Autocrine Growth Regulation

ELSEWHERE IN THIS ISSUE, Walsh and co-workers have reviewed the role of autocrine polypeptide growth factors in solid tumor malignancy.[1] The study of polypeptide growth factors has evolved rapidly in the past decade, and, as outlined by Walsh and colleagues, new concepts have emerged that contribute significantly to the understanding of the molecular pathogenesis of cancer. These advances have also revolutionized the study of embryogenesis and developmental biology, normal cellular growth, and the pathogenesis of diseases such as psoriasis and cirrhosis.

The rapid growth of this field has resulted in a new appreciation that most polypeptide growth factors can be catalogued into "gene families" or "gene superfamilies" on the basis of structural similarity; for example, the transforming growth factor (TGF)-β superfamily has more than 15 members with significant sequence identity and related biologic function.[2] With the discovery of a large number of related polypeptide growth factors, an intriguing redundancy in structure and function has also been identified. For example, despite localization of the three isoforms of human TGF-β (TGF-β_1, TGF-β_2, and TGF-β_3) to different chromosomes, the molecules bind the same receptors, share nearly identical biologic function, and have overlapping distribution in many tissues. It is also informative to note the markedly different tissue distribution of epidermal growth factor (EGF) and TGF-α, although these two related molecules share the same receptor and exhibit almost identical biologic activity. Even within a single tissue such as the developing mouse mammary gland, regional compartmentalization of TGF-α and EGF expression has been described, a finding that implies distinct functions.[3] Transforming growth factor-α and the EGF or TGF-α receptor are co-localized to the cap-cell layer of the terminal bud that makes up the proliferative zone within the ductal epithelium. In contrast, EGF is found only in mature luminal ductal cells of the mammary epithelium, suggesting a role in the regulation of fluid and electrolyte secretion. A challenge for the future will be understanding the redundancy of growth factor families and dissecting out distinct functions for the individual members.

Frequently a growth factor is named on the basis of the biologic activity that led to its discovery or the cell type in which it was initially identified. Pari passu with rapid advances in the identification of many new growth factors and the description of an expanded spectrum of biologic activity for these factors is the increasing recognition of the misleading nature of the nomenclature. For example, many "growth" factors are in fact potent inhibitors of growth, and the activities of epidermal growth factor and fibroblast growth factor extend beyond epithelial cells and fibroblasts, respectively. Although TGF-α and TGF-β are linked historically by their simultaneous identification in the conditioned medium of virally transformed cells, these molecules are not structurally or functionally related. Furthermore, both are produced by normal as well as transformed cells, and it is likely that the most important biologic role for these molecules is in the regulation of normal cell and tissue biology and physiology.[2] Notwithstanding, the study of polypeptide growth factors has emerged as one of the most exciting and productive areas in all of biomedical research.

Many existing and yet-to-be-discovered polypeptide growth factors will undoubtedly be characterized as "autocrine"; thus, it is useful to consider the definition of autocrine growth and how it can be studied or proved. An autocrine loop for modulating a cellular function exists when a cell type that synthesizes and secretes a polypeptide growth factor also has the capacity for biologic response to that same factor. In contrast to "endocrine" and "paracrine" pathways for growth regulation, autocrine growth control may occur in the context of a single cell or within a microenvironment of a few cells and may be difficult to prove or explore experimentally. Consequently, autocrine phenomena have been studied primarily in cell culture systems. While a demonstration of all the requisite elements for an autocrine loop—messenger RNA synthesis, protein secretion, binding to specific cell surface membrane receptors, signal transduction, and biologic response—constitutes supportive evidence for an autocrine pathway, a more stringent analysis requires the interruption of an autocrine loop at one or more points that results in ablation of the biologic response. This type of analysis requires highly specific reagents, stringent controls, and an awareness of redundancy in the system being studied.

Two examples that highlight the problem of redundancy follow. First, antibody-mediated blockade of the EGF or TGF-α receptor in a cell type that does not produce EGF does not prove TGF-α autocrine activity, as it is now recognized that amphiregulin (a recent addition to the EGF family) also binds to this receptor and has biologic activity similar to TGF-α and EGF.[4] Second, distinct receptors for gastrin-releasing peptide (GRP) and neuromedin B have been identified recently, and it appears that each ligand is capable of binding to both receptors, although with reduced affinity (J. F. Battey, MD, oral communication, June 1991).[5,6] The use of specific neutralizing antibodies or antisense constructs to the ligand itself is a preferred strategy to show autocrine activity convincingly. For example, Arteaga and associates have used neutralizing antibodies to TGF-β to demonstrate a negative autocrine loop in breast carcinoma cells.[7] The interruption of an autocrine loop at the level of mRNA translation using antisense constructs has not been reported, but this technique has been successfully applied in the study of proto-oncogene function.[8]

Experiments conducted in the isolated and controlled context of cell culture must be complemented by more physiologic studies in intact animals. Transgeneic animals provide an opportunity for this sort of analysis. Three recent and related studies have emphasized the utility of this experimental approach in understanding the biologic role of TGF-α in vivo. The overexpression of the normal TGF-α gene product in transgenic mice resulted in the development of mammary carcinoma in all of the studies,[9-11] as well as hepatocellular carcinoma in one of the reports.[10] These findings indicate that the overproduction of a naturally occurring growth factor in an in vivo context can result in neoplasia. Similar transgenic experiments using constructs containing tissue-specific promotors and other growth factors will undoubtedly serve as an important in vivo adjunct to the interpretation of studies done in cell culture.

In summary, the study of growth factors is a burgeoning field. Increasing evidence suggests that these polypeptides

play a major role in normal physiology. If disordered production contributes to neoplasia (perhaps by acting in an autocrine manner), it is plausible that innovative treatment strategies such as the use of growth factor receptor-blocking antibodies or growth factor-toxin linked conjugates may find a place in the armamentarium of those who battle cancer.

ROBERT J. COFFEY, MD
Associate Professor
Departments of Medicine and Cell Biology
Division of Gastroenterology

JOHN A. BARNARD, MD
Assistant Professor
Division of Pediatric Gastroenterology
Vanderbilt University School of Medicine
Nashville, Tennessee

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Correspondence

The Editors will be pleased to receive and consider for publication correspondence containing information of interest to physicians or commenting on issues of the day. Letters ordinarily should not exceed 600 words and must be typewritten, double-spaced, and submitted in duplicate (the original typescript and one copy). Authors will be given the opportunity to review the editing of their correspondence before publication.

Abortion 'Gag' Rule

To THE EDITOR: It is extremely disturbing that the Supreme Court has upheld the government regulation that physicians at family planning clinics receiving federal funds may not even mention the possibility of abortion to a woman. If they do, funding may be withheld.

This is not primarily an abortion issue.

It is not a religious issue—about half of Americans belong to religions that have no objections to abortion.

It is not a conservative versus liberal issue—John Kilpatrick, one of the nation's most conservative columnists, has denounced the Supreme Court's decision, for instance.

The real issues for physicians and patients are these:

- Abrogation of freedom of speech as guaranteed by the Constitution;
- Infringement upon the traditional and hitherto inviolable right of a physician to discuss freely all medical options with a patient; and
- Effective cancellation of the option of safe and legal abortions for low-income women.

This regulation currently is limited to abortion in federally funded family planning clinics, but who can foresee what future administrations will decide are unfit subjects for physicians to discuss with patients? The fact is that no one can predict what will result if this invasion of professional freedom is allowed to stand. The entire issue is fraught with uncharted and unpredictable dangers to the medical profession and to patients.

As I write this letter, there is a bill pending in Congress (HR 392) that, if passed, would negate this regulation. The probability is that this bill will pass. A Presidential veto is almost certain, however, unless there is vigorous opposition, and Congress probably will not be able to override the veto.

I strongly urge organized medicine and all physicians to write the President and request that he sign HR 392 as a protest against this extremely serious intrusion on the rights of free speech and professional freedom.

HERBERT NOTKIN, MD
2612 Hewitt Dr
Arcata, CA 95221

Do We Need Warning Labels on Food?

To THE EDITOR: As a family practitioner and full-time sports medicine physician, I was surprised by the commentary in the March 1991, "A Public Health Approach to Cholesterol," by Thomas Bodenheimer, MD, MPH.[1] He has made an effort to emphasize the consequences of elevated cholesterol on coronary heart disease (CHD) at the expense of common sense.

To suggest that low CHD rates in China and Japan are due to low-cholesterol and low-fat diets is to deny the role of heredity and life-style in coronary artery disease. To state that "ice cream, steak, and french fries are killers" is inflammatory and inaccurate. Diseases of the heart and cerebral vascular disease have dropped 44% and 65%, respectively, from 1950 to 1987, just in the years when fast food services were expanding.[2] Certainly many active persons using 2,000 to 3,000 calories a day could eat lean meat three to four times a week and remain well under fat intake limits set by the American Heart Association. Athletes and other active persons can also eat ice cream regularly without dying, if they choose other lower calorie and fat desserts regularly as well.

My concern is that athletes—women athletes and dancers specifically—are already at risk for iron deficiency and its consequences. They may be only further diverted from the best source of iron available to them—red meat. Women athletes are at risk for experiencing problems associated with iron deficiency due to increased demand associated with training and a possibility of compromised ability to use iron.[3-6] Diets inadequate in iron, often represented by modified vegetarian diets, have been shown to be related to amenorrhea in athletes.[4] Red meat has important elements of iron, zinc, and protein for an athlete's diet.

As the medical community seeks to improve health and make life-style changes, it is important that these changes be made with adequate scientific background.

ALVIN R. LOOSLI, MD
Center for Sports Medicine
1850 Mt Diablo Blvd, Suite 110
Walnut Creek, CA 94596

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* * *

To THE EDITOR: I read with interest Dr Bodenheimer's commentary on cholesterol in the March 1991 issue.[1]

I agree with Dr Bodenheimer's concern regarding our typical modern American approach to this problem. The National Cholesterol Education Program (NCEP) is emphasizing minor dietary change and then drugs, and we Americans are bombarded with the marketing of unhealthy foods. I believe the diagnosis of the problem is extreme, however, and the proposed solutions call for an unacceptable level of social control of people's lives and choices. The author suggests that our goal should be to have Americans' cholesterol levels down to a total cholesterol level of 150 mg per dl or lower. I would suggest that this goal is entirely impractical and that public health data suggest that most Americans with a total cholesterol level between 150 and 200 mg per dl have excel-

lent longevity. Dr Bodenheimer uses the word "medicalization" to describe the NCEP approach. I like this word and often use it as did Ivan Illich in his important book, *Medical Nemesis*. He describes the sickness of a society when people's lives become "medicalized" by a medical establishment rather than allowing for a freedom of choice in living. Dr Bodenheimer's public health approach represents medicalization even worse than the NCEP program. Following this advice, Americans would be bombarded with warning labels on most foods; there would be tight social control in advertising of foods and in excessive taxes. Food should not be medicalized beyond raising public awareness to the level of allowing all of us to make informed choices.

A more proper public health approach to preventive medicine, including a healthy diet, is through public education. I have long thought that we should *not* adopt a medical model for preventive medicine. Good preventive medical advice should be available in more than physicians' offices. Preventive medicine and health promotion should be in the public domain, with free and open access and widely available educational programs and articles. This is already occurring, and more people than ever are reducing the fat in their diets. Even McDonald's is bending to the pressure as it now introduces its new "McLean" burger. Some Americans will change; others will not.

We go over the line when we start treating food like cigarettes. I am a militant antismoker. Warning labels, prohibiting of advertising, and taxes are the most appropriate ways to attack cigarettes as the substance abuse that is the number one cause of premature death in America. Food should not be put in the same category. To do so would be imprudent, and to suggest doing so compromises our credibility in other important areas, such as cigarettes and safety (seat belt use). For many Americans, eating fatty food is a choice, and heart disease may be an eventual cause of death. That is really not so bad, since alternative causes of death are no more desirable.

JOSEPH E. SCHERGER, MD
Clinical Professor
Department of Medicine
University of California, Davis,
School of Medicine
Davis, CA 95616

REFERENCE

1. Bodenheimer T: A public health approach to cholesterol—Confronting the 'TV-auto-supermarket society.' West J Med 1991; 154:344-348

Dr Bodenheimer Responds

To the Editor: While making some good points about the complexity of nutritional interventions, Dr Loosli has interpreted my article somewhat loosely. I have not proposed a ban on red meat. Rather, I have suggested that "Foods classified by the federal government as high in calories, cholesterol, and saturated fats" should be regulated. Lean meats not classified as "high risk" foods would not require such regulation. Moreover, even without red meat, and accounting for lower iron absorption from vegetable sources, adults with high iron requirements can reach a plentiful daily total of 18 to 20 mg by consuming chicken, fish and shellfish, dried apricots and raisins, baked potatoes, whole wheat bread and breakfast cereals, plus adequate amounts of vitamin C, which enhances iron absorption.

Dr Loosli makes two errors in his statement about coronary heart disease (CHD) rates in China and Japan: While heredity does explain many interindividual differences in cholesterol levels, far more important are interpopulation differences, which are not hereditary in nature; the study of Japanese migrating to the United States, changing to an American-style diet, and suffering higher CHD rates confirms the link between rich diet and CHD. Also, he misses the fact that I affirm rather than deny the role of life-style (diet is a life-style factor) in CHD.

Dr Scherger presents his position in a logical manner; I simply disagree. We should not succumb to the therapeutic nihilism of Ivan Illich and accept that heart disease is not so bad because "we all gotta go somehow." The issue is, at what age do we die? Coronary heart disease strikes many people in the prime of their lives. Public education is fine as far as it goes, but it will not reach the educationally deprived lower income and minority populations. As with smoking, great divisions are developing in our society, with CHD rates dropping particularly for the middle and upper income groups. Many of our food habits come from the food industry, not from our own free choice. Reducing the availability of high-risk foods must be a central focus of our efforts to confront CHD in the most risk-laden sectors of our population. I sincerely hope that Dr Scherger rethinks his position.

THOMAS BODENHEIMER, MD, MPH
2517 San Bruno Ave
San Francisco, CA 94134

Lessons From the Practice

Routine Gone Awry

CARL COPPOLA, MD, *Los Angeles, California*

It was late at night, probably after 2 AM. Brittany, my 1-year-old daughter, was crying and wanted a bottle. Often I sleep through her crying, and my wife, Patti, tends to her, much to my wife's consternation. But tonight I woke up easily and slid out of bed before Patti could get to her. This night I especially wanted to hold her because by the time I had arrived home from work Brittany was already in bed.

I picked her up in my arms, and she immediately settled down in anticipation of a warm soothing bottle. The microwave chimed, signaling that all was ready. With bottle and child in hand, the two of us nestled down on the sofa in the peaceful dark. It felt so good to cuddle with her. With her rhythmic sucking, my mind began to drift. Today's events played back like a bad dream.

It was Saturday, the first of the month, and I was on call, starting my three-month rotation at Children's Hospital. I am a fourth-year resident in otolaryngology. Already I had considerable pediatric experience, a fact that gave me confidence in my new assignment. I met my predecessor at 7 AM on 6E to pick up the beeper and assume the service. She looked tired, as though she had been up all night. "You have a foreign body to do in a little while. She's 1½ years old with a coin at the cricopharyngeus. Should be routine. Why don't you do the case and then catch up with me on the wards?" We agreed, and off I went to the operating room.

After changing into scrubs, I found my patient in the preanesthesia holding area. Her name was Kelly. She had long brown hair and big brown eyes. She had a vivacious personality and was oblivious to the fact that she was the patient. She reminded me of my own little girl. Kelly kept talking away as we rolled her into the operating room. At this point most kids are frightened, but she thrived on the attention. She was very cooperative, which made anesthetizing her easy.

I have removed several dozen esophageal foreign bodies, mostly from children. Coins seem to be a particular favorite, especially pennies. We often try to guess the date, hoping to add a little adventure to a fairly "simple" case.

Kelly's vital signs were stable, normal sinus rhythm, 100% on the pulse oximeter, and completely paralyzed. My attending gave me the nod to proceed. Sure enough, it was a penny. I had it out in ten seconds. As was customary, I reinserted the esophagoscope to look for any erosions or other foreign bodies that might be lurking.

Suddenly all hell broke loose! Kelly's oxygen saturation fell, and an abnormal cardiac rhythm appeared on the monitor. I pulled the scope out and we ventilated her. Her chest moved easily with each compression of the bag, but now her blood pressure was bottoming out. Immediately my attending took over and confirmed the accurate position of the endotracheal tube. What had happened? And then, right before our eyes, she went asystole. What could have gone wrong?

Terror filled the room as we checked our lines and connections. The color around her lips and face made it clear there was nothing wrong with our monitors. I broke out into a cold sweat and began chest compressions. Frantically we worked to restore life to this helpless little girl.

We were 15 minutes into our resuscitation, and we still had no response! Beneath my hands her lifeless body lay, unresponsive to our pleas. I looked at her sweet young face. Just moments ago she had been entertaining us all with her innocent chatter. How could someone so alive, so full of energy, be knocking on death's door in such a short time? Was this really happening? I shuddered with fear. The thought of losing her brought tears to my eyes.

Miraculously, after 25 minutes we established a blood pressure and normal sinus rhythm. Her color returned to normal. And then we waited. How long was she anoxic? The whole room burst into a cheer when she reached for the tube to try to extubate herself. Somehow our prayers had been answered, and a tragedy had been avoided. Kelly went on to recover completely without any deficits. To this day, we still do not know what happened.

Later that day I realized that there is no such thing as a "simple" or "routine" procedure in medicine. We as physicians often take things for granted. Everything we do, no matter how benign it may seem to us, has implications for both patient and family.

Brittany's slurping signaled she was through with her bottle. Ordinarily I put her back in the crib and rush back to bed for more sleep. But this time I held her tightly through the night, long after she had fallen asleep.

* * *

"Lessons From the Practice" presents a personal experience of practicing physicians, residents, and medical students that made a lasting impression on the author. These pieces will speak to the art of medicine and to the primary goals of medical practice—to heal and to care for others. Physicians interested in contributing to the series are encouraged to submit their "lessons" to the series' editors.

JONATHAN E. RODNICK, MD
STEPHEN J. McPHEE, MD
Series' Editors

(Coppola C: Routine gone awry. West J Med 1991 Aug; 155:193)

From the Department of Otolaryngology, University of Southern California School of Medicine, and the Department of Otolaryngology-Head and Neck Surgery, Los Angeles County-USC Medical Center, Los Angeles.

Reprint requests to Carl Coppola, MD, Department of Otolaryngology, USC School of Medicine, 1200 N State St, Box 795, Los Angeles, CA 90033.

Poem

IN A CONVALESCENT HOSPITAL

I say, Lord, let her go.
Her flesh has melted underneath her skin;
The skin is bleached like leaves after the weight of snow
Slow winter month on month, mottled and shrunk,
And lined with swollen veins; her lips
Are fallen in upon her gums; and her white hair,
Grown thin as mist, lets show her skull.
Only her eyes are dark and bright,
And in a moment of full recognition, catch my gaze,
Full of surprise that I have come
Out of a day long passed, to bring my love.

I was a child and she was full of beauty,
Her long dark hair forever slipping from its combs.
By the low fire she laughed, and caught the coil,
And lifted it, still laughing, to her head,
And pinned it there;
The while my mother, smiling, chatted on,
Above the flutter of the little flames.

So well she sang! So patiently
From my embarrassed throat she coaxed a sound
Small credit to her patience. Still, she glowed,
Her eyes on mine, while her lips trembled
With the growing note
That from her own throat brightened, swelled,
And rounded, and grew dim. All this
To teach a troubled child to sing.

Now she speaks hurriedly,
In sudden panic clutching at my hand. Oh,
Let me out of here! Where am I? Here?
I don't belong here. Let me go!
And I? What can I say? Lord, let her go?
Yet who am I to say, Lord, let her go?

Why is she here, and why
Am I here with her to remember joy?
What can I know
Of gentleness engendered by her need,
Of charity bestowed
By those who never saw her young?
They come and go in rounds impersonal, prescribed,
Prescribed, and even paid for, yet are kind.

I take this moment for its preciousness,
In grief for her, for me,
And pray it bless
Both her, and me.

JANET LEWIS©
Los Altos, California

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Our readership represents all specialties of medicine. We wish to receive and publish manuscripts that are valid, important, lively, well-written, and succinct. They should be of interest to a broad range of busy practitioners, students, researchers, and scholars who have a clinical orientation. The purpose of a paper or letter may be to alert, review, discuss—above all, to teach. Titles should be short and intriguing. Avoid jargon, the overuse of abbreviations and acronyms, sexist language, redundancies, or expendable words and phrases (see *AMA Manual of Style,* 8th Edition).

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Abbreviations of journal titles should conform to those used in *Index Medicus*. List up to six authors; for seven or more, use et al after listing the first three.

1. Jones JS, Anderson HW Jr, Johnson DW, et al: The athletic heart revisited—Sudden death of a 28-year-old athlete. JAMA 1978; 292:444-456

2. Berman SM, Shah B, Wyle FA, Dacosta-Iyer M, McRae DM: Disseminated *Pneumocystis carinii* in a patient receiving aerosolized pentamidine prophylaxis. West J Med 1990; 153:82-86

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4. Munsung JD: The role of drugs, chap 2, *In* Brest AN, Mayer JD (Eds): Hypertension—Vol 3, Therapy, 2nd Ed. Chicago, Ill, Year Book Medical Publishers, 1961, pp 456-479 (authors of book differ from chapter author)

Correspondence

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8. O'Connell M: A Controlled Trial of Regional Intra-arterial FUDR Versus Systemic 5FU for the Treatment of Metastatic Colorectal Cancer Confined to the Liver. Presented at the annual meeting of the American Society of Clinical Oncology, San Francisco, December 1989

Mass Circulation Publications (Do not include in reference list; put in text)

(T. Harris, "Selenium-Rich Sediments Also Have Been Reported in Wildlife Refuges," *The Sacramento Bee*, September 8, 1985, p 5)

Personal Communications and Unpublished Data

This material should not be included in the reference list but should be given in parentheses in the body of the text, listing the person's name, highest academic degrees, and professional affiliation, whether the communication was oral or written, and the date (month and year).

Lyme disease has been reported in red squirrels (J. Sneed, PhD, Department of Wildlife, written communication, September 1990).

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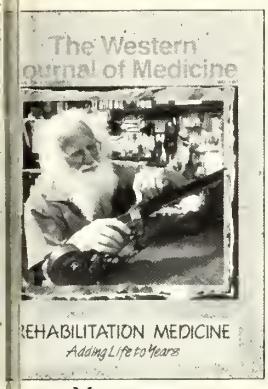

MAY 1991

REHABILITATION MEDICINE *Adding Life to Years*

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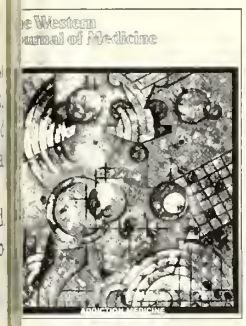

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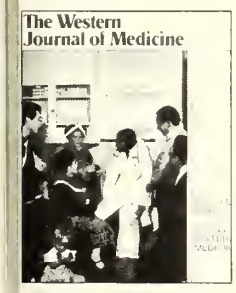

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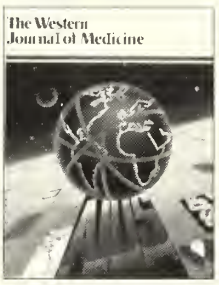

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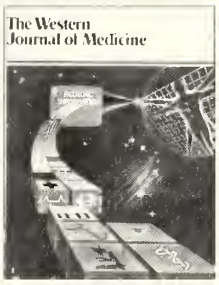

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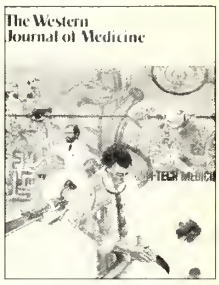

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(Continued from Page 131)

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. Accredited institutions wishing to list AMA Category 1 CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, UT 84102; or phone (801) 355-5290. For information on CME accreditation, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution.

MEDICAL GRAND ROUNDS

Each Wed—8:00-9:00 a.m. Alternating between University of Utah Medical Center and VA Medical Center, Salt Lake City. Contact: William D. Odell, MD, PhD, Professor and Chairman, Dept of Internal Medicine, Univ of Utah, (801) 581-7606.

* * *

September 27-29—**Laser Surgery—Laparoscopic Cholesystectomy** (Sponsor: UUSM). Fri-Sun. The Laser Institute, University of Utah, Salt Lake City. Contact: (801) 581-7001.

November 15-16—**Laser Surgery—Laparoscopic Cholesystectomy** (Sponsor: UUSM). Fri-Sat. The Laser Institute, University of Utah, Salt Lake City. Contact: (801) 581-7001.

SPONSORS OF COURSES—ABBREVIATIONS

AHA: American Heart Association, Utah Affiliate, 645 E 400 South, Salt Lake City 84102. (801) 322-5601.

CH: Castleview Hospital (formerly Carbon Hospital), RFD 2, Box 46, Price 84501. (801) 637-4800.

HCH: Holy Cross Hospital, 1045 E First South, Salt Lake City 84102. (801) 350-4744.

ITS: Intermountain Thoracic Society, 1616 S 11th East, Salt Lake City 84105. (801) 484-4456.

LDSH: LDS Hospital, 8th Ave and "C" St, Salt Lake City 84143. (801) 321-1100.

LRH: Logan Regional Hospital, 1400 N 5th East, Logan 84321. (801) 752-2050.

MDH: McKay-Dee Hospital Center, 3939 Harrison Blvd, Ogden 84409. (801) 399-4141.

MVH: Mountain View Hospital, 1000 E Highway 6, Payson 84651. (801) 465-9201.

144: 144th Evacuation Hospital, PO Box 8000, Salt Lake City 84108. (801) 524-3924.

OSS: Ogden Surgical Society, PO Box 9311, Ogden 84409.

PVH: Pioneer Valley Hospital, 3460 S 4155 West, West Valley City 84120. (801) 968-9061.

UOS: Utah Ophthalmological Society, 540 E 500 South, Salt Lake City 84102. (801) 355-7477.

USH: Utah State Hospital, PO Box 270, Provo 84603-0270. (801) 373-4400.

UUSM: University of Utah School of Medicine, Office of Continuing Medical Education, 50 N Medical Dr, Salt Lake City 84132. (801) 581-8664.

VAMC: Veterans Administration Medical Center, 500 Foothill Dr, Salt Lake City 84148. (801) 582-1565.

VVMC: Valley View Medical Center, 595 S 75 East, Cedar City 84720. (801) 586-6587.

WRI: Western Rehabilitation Institute, 8074 S 1300 East, Sandy 84094. (801) 561-3400.

WASHINGTON

The listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here, please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle, WA 98121; or phone (206) 441-WSMA.

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

August 15-18—**World Gathering on Bereavement.** Kirkland. Thurs-Sun. Contact: Evergreen Hospital, (206) 878-3710.

August 17-18—**Advanced Cardiac Life Support.** Seattle. Sat-Sun. Contact: VMMC.

August 23-25—**ACCME Regional Workshop.** Seattle. Fri-Sun. Contact: U/W.

September 12-13—**Resolving the Ethical Dilemmas in Animal Protocol Review.** Seattle. Thurs-Fri. Contact: U/W.

September 13—**New Therapies in Hepatobiliary Disease.** Seattle. Fri. Contact: VMMC.

September 16-20—**Family Practice Review.** Seattle. Mon-Fri. Contact: U/W.

September 20-21—**Practical Management of Substance Abuse.** Seattle. Thurs-Fri. Contact: U/W.

September 26—**Cardiology Update.** Everett. Thurs. Contact: Pacific Northwest Medical Education Institute, (206) 258-6322.

September 27—**Surgery Update.** Seattle. Fri. Contact: U/W.

October 5—**2nd Annual Practice Update for Rural Physicians.** Seattle. Sat. Contact: VMMC.

October 10-12—**Burn Update.** Seattle. Thurs-Sat. Contact: U/W.

October 17-19—**Endoscopic Sinus Surgery.** Seattle. Thurs-Sat. Contact: U/W.

October 18—**Atypical Pneumonia Syndromes.** Seattle. Fri. Contact: VMMC.

October 18-20—**Spinal Cord Injury.** Seattle. Fri-Sun. Contact: U/W.

October 24—**Geriatrics.** Everett. Thurs. Contact: Pacific Northwest Medical Education Institute, (206) 258-6322.

November 1—**Radiosurgery Update.** Seattle. Fri. Contact: VMMC.

November 7-8—**Drug Update: Prescription for the '90s.** Seattle. Thurs-Fri. Contact: (206) 258-6322.

November 8—**25th Annual Cancer Conference.** Seattle. Fri. Contact: VMMC.

November 14-15—**Drug Therapy.** Seattle. Thurs-Fri. Contact: U/W.

December 6—**Practical Pediatrics.** Seattle. Fri. Contact: VMMC.

December 6-7—**Urology.** Seattle. Fri-Sat. Contact: (206) 441-9762.

December 12-14—**American College of Physicians.** Seattle. Thurs-Sat. Contact: U/W.

December 12-14—**7th Annual ID Conference.** Everett. Thurs-Sat. Contact: Pacific Northwest Medical Education Institute, (206) 258-6322.

COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Avenue, Seattle, WA 98104. (206) 223-5953.

PCMS CME—Contact: Mrs Maxine Bailey, Executive Director, College of Medical Education, 705 South Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON)—Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

WSMA—Washington State Medical Association, Continuing Medical Education, 2033 Sixth Ave, Suite 900, Seattle, WA 98121. (206) 441-9762.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, PO Box 900, Seattle, WA 98111. (206) 223-6898.

WYOMING

October 25-26—**14th Annual Perinatal Conference.** Children's Hospital of Denver at Laramie. Fri-Sat. Contact: Christine Sievers-Spencer, (303) 861-6413. ◆

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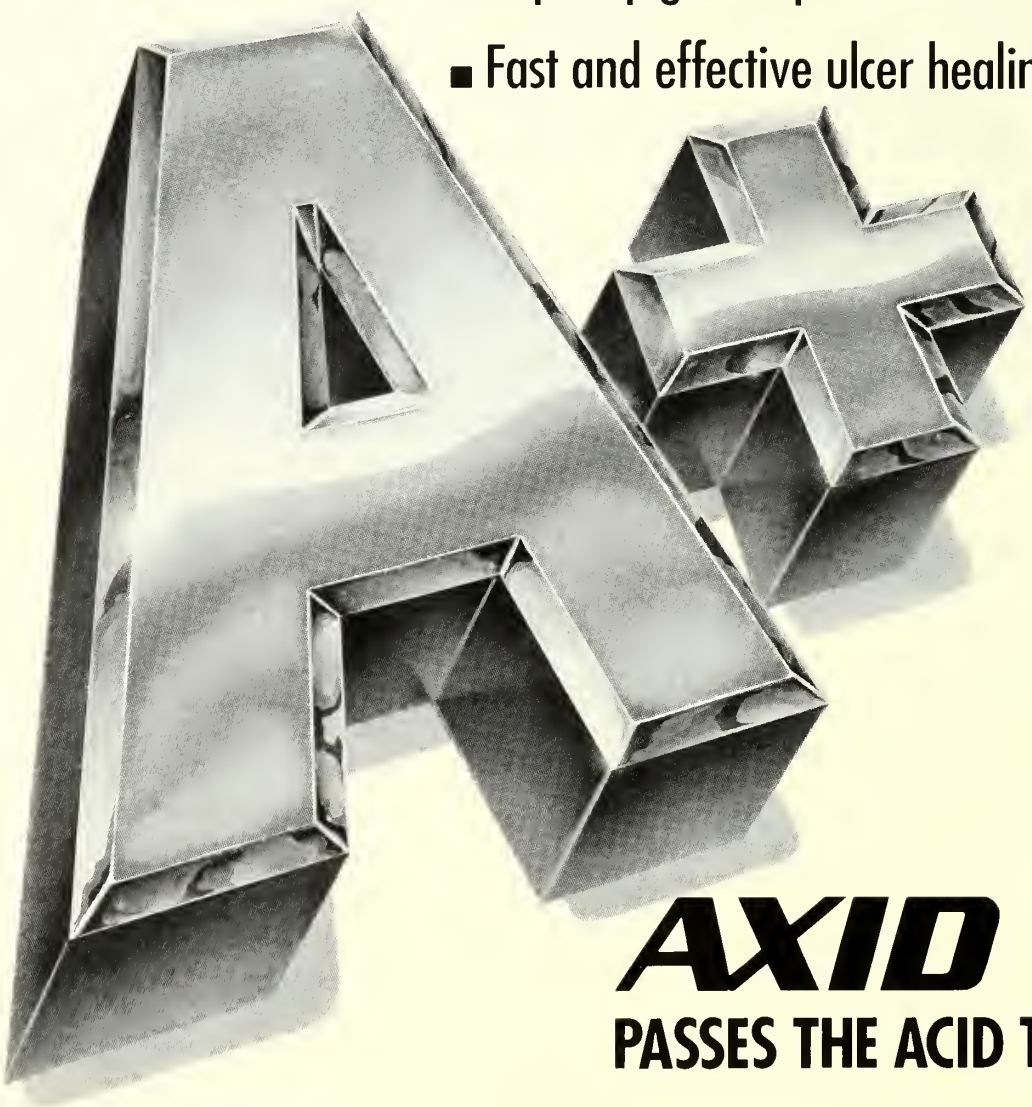

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Brief Summary. Consult the package insert for complete prescribing information.
Indications and Usage: 1 *Active duodenal ulcer*—for up to 8 weeks of treatment. Most patients heal within 4 weeks.

2 *Maintenance therapy*—for healed duodenal ulcer patients at a reduced dosage of 150 mg h.s. The consequences of therapy with Axid for longer than 1 year are not known.

Contraindications: Known hypersensitivity to the drug. Because cross sensitivity in this class of compounds has been observed, H_2-receptor antagonists, including Axid, should not be administered to patients with a history of hypersensitivity to other H_2-receptor antagonists.

Precautions: *General*—1. Symptomatic response to nizatidine therapy does not preclude the presence of gastric malignancy.

2. Dosage should be reduced in patients with moderate to severe renal insufficiency.

3. In patients with normal renal function and uncomplicated hepatic dysfunction, the disposition of nizatidine is similar to that in normal subjects.

Laboratory Tests—False-positive tests for urobilinogen with Multistix® may occur during therapy.

Drug Interactions—No interactions have been observed with theophylline, chlordiazepoxide, lorazepam, lidocaine, phenytoin, and warfarin. Axid does not inhibit the cytochrome P-450 enzyme system, therefore, drug interactions mediated by inhibition of hepatic metabolism are not expected to occur. In patients given very high doses (3,900 mg) of aspirin daily, increased serum salicylate levels were seen when nizatidine, 150 mg b.i.d., was administered concurrently.

Carcinogenesis, Mutagenesis, Impairment of Fertility—A 2-year oral carcinogenicity study in rats with doses as high as 500 mg/kg/day (about 80 times the recommended daily therapeutic dose) showed no evidence of a carcinogenic effect. There was a dose-related increase in the density of enterochromaffin-like (ECL) cells in the gastric oxyntic mucosa. In a 2-year study in mice, there was no evidence of a carcinogenic effect in male mice, although hyperplastic nodules of the liver were increased in the high-dose males as compared with placebo. Female mice given the high dose of Axid (2,000 mg/kg/day, about 330 times the human dose) showed marginally statistically significant increases in hepatic carcinoma and hepatic nodular hyperplasia with no numerical increase seen in any of the other dose groups. The rate of hepatic carcinoma in the high-dose animals was within the historical control limits seen for the strain of mice used. The female mice were given a dose larger than the maximum tolerated dose, as indicated by excessive (30%) weight decrement as compared with concurrent controls and evidence of mild liver injury (transaminase elevations). The occurrence of a marginal finding at high dose only in animals given an excessive and somewhat hepatotoxic dose, with no evidence of a carcinogenic effect in rats, male mice, and female mice (given up to 360 mg/kg/day, about 60 times the human dose), and a negative mutagenicity battery are not considered evidence of a carcinogenic potential for Axid.

Axid was not mutagenic in a battery of tests performed to evaluate its potential genetic toxicity, including bacterial mutation tests, unscheduled DNA synthesis, sister chromatid exchange, mouse lymphoma assay, chromosome aberration tests, and a micronucleus test.

In a 2-generation, perinatal and postnatal fertility study in rats, doses of nizatidine up to 650 mg/kg/day produced no adverse effects on the reproductive performance of parental animals or their progeny.

Pregnancy—Teratogenic Effects—Pregnancy Category C—Oral reproduction studies in rats at doses up to 300 times the human dose and in Dutch Belted rabbits at doses up to 55 times the human dose revealed no evidence of impaired fertility or teratogenic effect; but, at a dose equivalent to 300 times the human dose, treated rabbits had abortions, decreased number of live fetuses, and depressed fetal weights. On intravenous administration to pregnant New Zealand White rabbits, nizatidine at 20 mg/kg produced cardiac enlargement, coarctation of the aortic arch, and cutaneous edema in 1 fetus; and at 50 mg/kg, it produced ventricular anomaly, distended abdomen, spina bifida, hydrocephaly, and enlarged heart in 1 fetus. There are, however, no adequate and well-controlled studies in pregnant women. It is also not known whether nizatidine can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Nizatidine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers—Studies in lactating women have shown that 0.1% of an oral dose is secreted in human milk in proportion to plasma concentrations. Because of growth depression in pups reared by treated lactating rats, a decision should be made whether to discontinue nursing or the drug, taking into account the importance of the drug to the mother.

Pediatric Use—Safety and effectiveness in children have not been established.

Use in Elderly Patients—Healing rates in elderly patients were similar to those in younger age groups as were the rates of adverse events and laboratory test abnormalities. Age alone may not be an important factor in the disposition of nizatidine. Elderly patients may have reduced renal function.

Adverse Reactions: Clinical trials of varying durations included almost 5,000 patients. Among the more common adverse events in domestic placebo-controlled trials of over 1,900 nizatidine patients and over 1,300 on placebo, sweating (1% vs 0.2%), urticaria (0.5% vs <0.01%), and somnolence (2.4% vs 1.3%) were significantly more common with nizatidine. It was not possible to determine whether a variety of less common events were due to the drug.

Hepatic—Hepatocellular injury (elevated liver enzyme tests or alkaline phosphatase) possibly or probably related to nizatidine occurred in some patients. In some cases, there was marked elevation (>500 IU/L) in SGOT or SGPT and, in a single instance, SGPT was >2,000 IU/L. The incidence of elevated liver enzymes overall and elevations of up to 3 times the upper limit of normal, however, did not significantly differ from that in placebo patients. All abnormalities were reversible after discontinuation of Axid. Since market introduction, hepatitis and jaundice have been reported. Rare cases of cholestatic or mixed hepatocellular and cholestatic injury with jaundice have been reported with reversal of the abnormalities after discontinuation of Axid.

Cardiovascular—In clinical pharmacology studies, short episodes of asymptomatic ventricular tachycardia occurred in 2 individuals administered Axid and in 3 untreated subjects.

CNS—Rare cases of reversible mental confusion have been reported.

Endocrine—Clinical pharmacology studies and controlled clinical trials showed no evidence of antiandrogenic activity due to nizatidine. Impotence and decreased libido were reported with equal frequency by patients on nizatidine and those on placebo. Gynecomastia has been reported rarely.

Hematologic—Fatal thrombocytopenia was reported in a patient treated with nizatidine and another H_2-receptor antagonist. This patient had previously experienced thrombocytopenia while taking other drugs. Rare cases of thrombocytopenic purpura have been reported.

Integumental—Sweating and urticaria were reported significantly more frequently in nizatidine- than in placebo-treated patients. Rash and exfoliative dermatitis were also reported.

Hypersensitivity—As with other H_2-receptor antagonists, rare cases of anaphylaxis following nizatidine administration have been reported. Rare episodes of hypersensitivity reactions (eg, bronchospasm, laryngeal edema, rash, and eosinophilia) have been reported.

Other—Hyperuricemia unassociated with gout or nephrolithiasis was reported. Eosinophilia, fever, and nausea related to nizatidine have been reported.

Overdosage: Overdoses of Axid have been reported rarely. If overdosage occurs, activated charcoal, emesis, or lavage should be considered along with clinical monitoring and supportive therapy. Renal dialysis does not substantially increase clearance of nizatidine due to its large volume of distribution.

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References
1. Data on file, Lilly Research Laboratories
2. *Scand J Gastroenterol* 1987,22(suppl 136):61-70.
3. *Scand J Gastroenterol* 1987,22(suppl 136):47-55.
4. *Am J Gastroenterol* 1989,84:769-774

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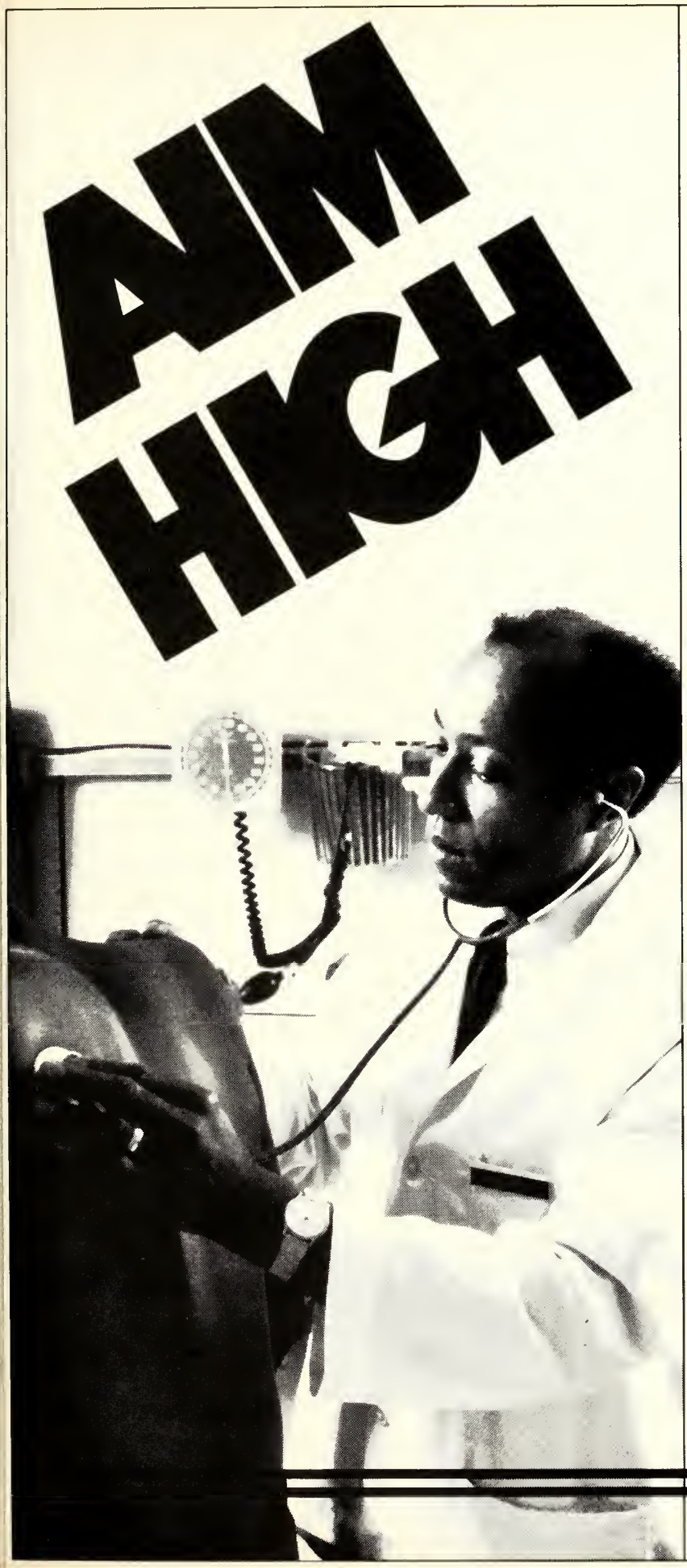
EMERGENCY MEDICINE. Emergency Medicine group seeking career oriented ACLS, ATLS certified physician for an immediate opening. Moderate volume; income $140,000 plus. Great outdoor activities including hunting, fishing, boating, skiing, sailing, camping, and hiking in south central Washington on the Columbia River. Send CV to Kennewick Emergency Physicians, PS, PO Box 6192, Kennewick, WA 99336-6192; or call (509) 627-1798.

(Continued on Page 204)



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(Continued from Page 202)

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For all specialties for hospitals, clinics, multi-specialty groups, partnership and solos. Contact Jim Grant in complete confidence at the bay area specialists. **G & G Physician Services, 1400 Coleman, Ste B-22, Santa Clara, CA 95050; or call (800) 727-2478, FAX # (408) 727-7390.** Never a fee to the physician.

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WASHINGTON. Openings for career oriented Emergency Physicians, BC in Emergency or Primary medical specialty. Seattle metropolitan hospital with 54,000 annual visits. Excellent salary in a stable growing group. Contact Dan Hiatt in care of Linda Johnson, 8009 S. 180th, Ste 110, Kent, WA 98032; (206) 575-2595.

MEDICAL DIRECTOR. Family Practice Physician (BC/BE) for community based clinic. Emphasis Family Planning, Primary Care, Pediatrics, STD and health education. Responsibile for medical policy, QA, and supervision of clinical staff. Bilingual/cultural Hispanic preferred. Inquiries to EVCC, 2470 Alvin Ave, #3, San Jose, CA 95121. EOE.

OTOLARYNGOLOGIST. BC/BE to join 28 physician multispecialty group practice. Located in beautiful Pacific northwest between Seattle and Vancouver, BC. Contact Shane Spray, 1400 E. Kincaid, Mount Vernon, WA 98273.

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BC/BE FAMILY PRACTITIONER, OB-competent, for nonprofit community clinic in California redwood country. Rural but sophisticated university town. Contact Donald Verwayen, Northcountry Clinic, 785 18th St, Arcata, CA 95521; (707) 822-2481.

INTERNIST. Immediate opening. Large, established, rapidly growing Los Angeles medical facility. High salary. Full benefits. Malpractice insurance paid. Contact Mr Miller; (213) 384-2504.

PATHOLOGIST, BC/BE—CENTRAL CALIFORNIA VALLEY. Seven member group seeks associate for independent multiple hospital and private laboratory practice. Send CV to Robert F. Chard, MD, Delta Pathology Associates Medical Group, 2291 W. March Ln, Ste 179E, Stockton, CA 95207.

FAMILY PRACTICE RESIDENCY FACULTY POSITION—CASPER, WYOMING. University of Wyoming Family Practice Residency-Casper is seeking an experienced, clinically oriented, BC Pediatrician to be the Pediatric Coordinator of an 8-8-8 Family Practice residency program. Level II Nursery skills are a must. 60% teaching, 20% direct patient care, 20% research. This is a tenure track position. University approval will be required prior to filling this position. Come join us in beautiful Wyoming. The University of Wyoming is an affirmative action/EOE. Contact Dr David Driggers, Director, University of Wyoming Family Practice Residency, 1522 E. "A" St, Casper, WY 82601; (307) 266-3076.

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OREGON. General Internal Medicine and Family Practice, BC/BE, sought for 10 member, multispecialty group in beautiful rural community, population 16,500, 38 miles southwest of Portland. Send CV to Administrator, 420 E. Fifth St, McMinnville, OR 97128; (503) 472-6161.

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FAMILY PRACTICE, BC/BE to join group practice in growing southwestern town. Full service clinic, 280-bed hospital. Offering competitive salary, equal call schedule, partnership. Contact Myrna Hughes, Arizona Western Medical Center, 2149 W. 24th St, Yuma, AZ 85364; (602) 344-1400.

PEDIATRICIAN, BC/BE to join group Family Practice/Pediatrics. Growing community with growing pediatric population. Active Nursery Level II hospital and nursery with NNP coverage. Offering competitive salary, equal call schedules, partnership. Contact Myrna Hughes, Arizona Western Medical Center, 2149 W. 24th St, Yuma, AZ 85364; (602) 344-1400.

MEMORIAL CLINIC offers excellent opportunity for BC/BE Family Practitioner to establish a second Family Practice neighborhood clinic. OB optional. Competitive salary and excellent benefits. Send CV to Memorial Clinic, Attention Inge Hart, 500 Lilly Rd, N.E., Olympia, WA 98506; (206) 456-1122, ext 249.

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If you are committed to excellence and strongly motivated for success, we would like to hear from you. Please send your CV to Maureen Forrester, San Jose Medical Group, Inc, 45 S 17th St, San Jose, CA 95112; **or call (408) 282-7833.**

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OB/GYN—Southern California. Career opportunities for ambitious Obstetricians desiring private practice. Growing, prestigious, university-affiliated south bay medical center is recruiting BC/BE Physicians for expanding solo and group practices. Excellent compensation. Submit CV to J. Michaels, 2600 Cliff Dr, Newport Beach, CA 92663.

PEDIATRICIANS—Southern California. Challenging career opportunities for Pediatricians desiring private practice. Growing, prestigious, university-affiliated south bay medical center is recruiting BC/BE physicians for expanding solo and group practices. Excellent compensation. Submit CV to J. Michaels, 2600 Cliff Dr, Newport Beach, CA 92663.

ORTHOPEDIC SURGEONS. Orthopedic Surgeon for busy Orthopedic service in 223-bed teaching hospital with residencies in General Surgery, Internal Medicine, OB/GYN, and Family Practice. Should be BC/BE. Experience in Arthroscopy preferred. Salary and compensation plan negotiable depending on experience. Hospital located in beautiful northern San Joaquin valley close to major cities and skiing areas. Please submit CV and references or contact Nathaniel Matolo, MD, Chief of Surgery, San Joaquin General Hospital, PO Box 1020, Stockton, CA 95201; (209) 468-6600. AA/EOE.

KETCHIKAN, ALASKA. University of Washington-affiliated Family Practice seeking BC Family Physician interested in teaching and providing excellent medical care. Accredited hospital in scenic southeast Alaska. 12 years of Family Medicine students and residents through WAMI program. Fee-for-service practice. Comprehensive benefits. Negotiable salary. Stable community with wide range of activities and opportunities. Contact David Johnson, MD, or Bill Henrickson, MD, Ketchikan Medical Clinic, Inc, 3612 Tongass Ave, Ketchikan, AK 99901; phone collect (907) 225-5145.

(Continued on Page 205)

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PHYSICIANS WANTED

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CALIFORNIA MULTISPECIALTY. Dermatologist, Radiologist, Otorhinolaryngologist, General Surgeon, Cardiologist, Internal Medicine, Pediatrician, Gastroenterologist, Orthopedist, General/Family Practitioner, Obstetrician/Gynecologist. Excellent opportunity for physicians in Los Angeles suburb to join 100 member multispecialty medical group. Large fee-for-service and prepaid practice, no Medi-Cal. Excellent compensation program based on guarantee plus incentive, profit sharing and pension plan. Group provides health, dental, life, and malpractice. Partnership in real estate and medical corporation available. Send CV to Ron McDaniel, Assistant Administrator, Mullikin Medical Center—5, 17821 S. Pioneer Blvd, Artesia, CA 90701.

CALIFORNIA MEDICAL/LEGAL DISABILITY EVALUATIONS opportunities available in San Jose and Fremont, California for BC physicians in Orthopedics, Neurology, Ophthalmology, Otolaryngology, Psychiatry, Toxicology, and Cardiology with multispecialty forensic medical evaluation group. Practice limited to evaluations. Excellent opportunity to supplement income. Send inquiry and CV to Martie Woodson, QMA, 39039 Paseo Padre Pkwy, Fremont, CA 94538; (415) 792-7271.

DIAGNOSTIC RADIOLOGIST. Position for a BC Radiologist to provide sole coverage for a 27-bed hospital in a southeast Idaho community of 20,000. Immediate potential for a $220,000 practice while still having time to enjoy geographical amenities. Contract available. Please call or write Randall G. Holom, 1224 8th St, Rupert, ID 83350; (208) 436-0481.

(Continued on Page 206)

(Continued from Page 205)

PHYSICIANS WANTED

DENVER PSYCHIATRISTS. Progressive suburban Denver, public and private, CMHC has full- and part-time openings in varied and challenging positions. Openings include outpatient, inpatient, and partial hospitalization. These can be put together in interesting combinations that eliminate boring and repetitive work. Salaries are competitive and benefits include malpractice, health, dental, and life insurance with liberal retirement, maternity and leave policies. Contact Robert J. Nathan, MD, Medical Director, Jefferson Center for Mental Health, 5265 Vance St, Arvada, CO 80002; (303) 425-0300. EOE M/F/H/V.

NORTHERN CALIFORNIA GENERAL SURGEON. Opportunity for General Surgeon with thoracic and vascular experience. Salary leading to partnership. Surgical group in northern California rural community. Excellent quality of life. Reply to 1165 S Dora, Ste A-3, Ukiah, CA 95482; (707) 462-7579.

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SAN FRANCISCO BAY AREA. Energetic, recently trained BC/BE General Internist needed for 12 MD satellite of Palo Alto Medical Clinic, a 150 physician multispecialty group with a national reputation for innovation and excellence. Broad inpatient/outpatient Internal Medicine practice in growing bay area community. Excellent location with convenient access to San Francisco and Stanford. Competitive compensation/benefits package. Early partnership. Please send CV to David Hooper, PAMC Fremont Center, 39500 Liberty St, Fremont, CA 94538.

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MONTEREY BAY. Immediate opportunity for full-time/part-time Internist/Family Practitioner to join busy, well established and respected group practice. Excellent laboratory and x-ray facilities. Send CV to Thorngate Medical Group, attn. Jean Reynolds, 1011 Cass St, Ste 201, Monterey, CA 93940.

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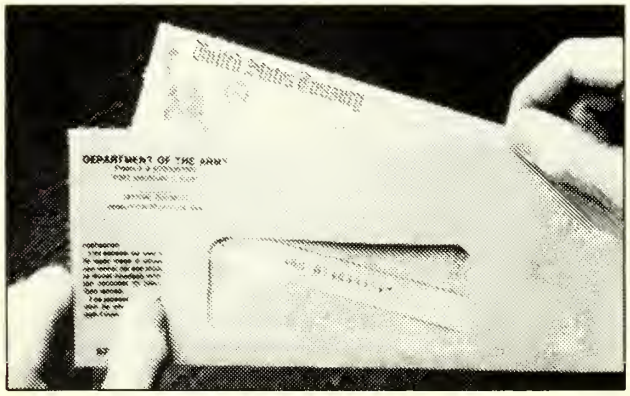

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(Continued on Page 207)

(Continued from Page 206)

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CALIFORNIA. Physician Recruiting Services available to solo practitioners, single and multispecialty clinics, and hospitals. Placement positions available in Family Practice, Dermatology, Internal Medicine, OB/GYN, Neurology, General Surgery, and others. For information call Bradshaw Associates, 21 Altamount, Orinda, CA 94563; (415) 376-0762.

SAN FRANCISCO AREA. Multiple practice opportunities in desirable suburb. Near water and mountains for recreation. Partnership, Family Practice group—urgicenter. Excellent compensation package. Call Pat Wall at (800) 462-1857.

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NORTHERN CALIFORNIA. Two multispecialty groups seeking BC/BE General Internist, OB/GYN, Pediatrician, Neurologist, and Orthopedic Surgeon for growing clinics in Marin and San Mateo counties. Reasonable call schedule. Competitive salary and benefits. Send CV to Number 242, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

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(Continued on Page 208)

(Continued from Page 207)

Western States OPENINGS

Many multispecialty groups and hospitals have asked us to recruit for over 300 positions of various specialties. Both permanent and locum tenens. Send CV to **Western States Physician Services, 5627 E. Kings Canyon, Ste 156, Fresno, CA 93727, or call 1 (800) 873-0786.**

ACTIVE TWO PERSON FAMILY PRACTICE seeking third partner. Full spectrum care with excellent hospital and specialist support. Local schools are excellent in this beautiful waterfront community adjacent to the San Juan Islands, Mt. Baker, fishing, skiing, and sailing. One hour from Seattle or Vancouver, B.C. Contact Mike James, MD; (206) 293-6642.

BC/BE DIAGNOSTIC RADIOLOGIST needed immediately for small two person rural office and hospital practice in northeastern Oregon. X-ray, ultrasound, nuclear medicine, CT, mammo, with mobile MRI in the works. Contact Beverly Jahncke; (503) 276-2431.

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BE/BC UROLOGIST to join busy 28 doctor multispecialty group practice. Excellent practice opportunity, full range of benefits, early partnership status. For more information contact Shane Spray, 1400 Kincaid, Mount Vernon, WA 98273; (206) 428-2524.

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(Continued on Page 209)

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(Continued from Page 208)

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(Continued on Page 210)

(Continued from Page 209)

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Colorado Medical Society—PO Box 17550, Denver 80217-0550. (303) 779-5455. Annual Meeting: September 20-22, 1991, Snowmass.

Hawaii Medical Association—1360 S Beretania, Honolulu 96814. (808) 536-7702. Annual Meeting: October 11-13, 1991, Westin Kauai.

Idaho Medical Association—305 W Jefferson, PO Box 2668, Boise 83701. (208) 344-7888. Annual Meeting: 1992, date and location to be announced.

Montana Medical Association—2012 11th Ave, Suite 12, Helena 59601. (406) 443-4000. Annual Meeting: October 3-4, 1991, Kalispell.

Nevada State Medical Association—3660 Baker Lane, Reno 89502. (702) 825-6788. Annual Meeting: 1992, date and location to be announced.

New Mexico Medical Society—7770 Jefferson, Suite 400, Albuquerque 87109. (505) 828-0237. Annual Meeting: 1992, date and location to be announced.

Oregon Medical Association—5210 SW Corbett Ave, Portland 97201. (503) 226-1555. Annual Meeting (House of Delegates only): 1992, date and location to be announced.

Utah Medical Association—540 E Fifth South, Salt Lake City 84102. (801) 355-7477. Annual Meeting: September 11-13, 1991, University Park Hotel, Salt Lake City.

Washington State Medical Association—900 United Airlines Bldg, 2033 6th Ave, Seattle 98121. (206) 441-WSMA. Annual Meeting: September 19-22, 1991, Red Lion, Bellevue.

Wyoming Medical Society—PO Drawer 4009, Cheyenne 82003-4009. (307) 635-2424. Annual Meeting: 1992, date and location to be announced.

ADVERTISING INDEX

BLUE CROSS OF CALIFORNIA 119

CENTURY CITY HOSPITAL
West Coast Spine Institute 201

CIBA-GEIGY PHARMACEUTICALS 123

CIGNA HEALTHPLAN 208

CLASSIFIED ADVERTISING 202, 204, 205, 206, 207, 208, 209, 210

COLUMBINE HOSPITAL
Eating Treatment Center 199

ELI LILLY & COMPANY
Axid 200, 201

FHP HEALTH CARE 207

HOFFMANN LA ROCHE LABORATORIES
Librax 128, 129
Valium . . . . . 3rd and 4th covers

LOCKHEED MISSILES & SPACE COMPANY 205

MARION MERRELL DOW INC.
Cardizem 115, 116
Nicarette . . . . . 2nd cover, 107, 108

MEAD JOHNSON PHARMACEUTICAL DIVISION
BuSpar 113, 114

PALISADES PHARMACEUTICALS INC.
Yacan 108

ST. VINCENT MEDICAL CENTER 126

G.D. SEARLE & COMPANY
Calan SR 121

SMITHKLINE BEECHAM PHARMACEUTICALS
Augmentin 125, 126
Tagamet 131, 132

UNIVERSITY MICROFILM 114

UNIVERSITY SOUTHERN CALIFORNIA
University Hospital 111

US AIR FORCE 203

US ARMY RESERVE 206

THE WESTERN JOURNAL OF MEDICINE
Special Issues 197
Subscription 130

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The Western Journal of Medicine

VOLUME 155 • NUMBER 3 SEPTEMBER 1991

BIOMEDICAL SCIENCE

249 Causes and Prevention of Calcium-containing Renal Calculi
R A L SUTTON

ARTICLES

253 Angiographic Yield in Penetrating Extremity Trauma
V HENDERSON, R NAMBISAN, M E SMITH, K K YIM, and C H ORGAN Jr

256 Leg Symptoms in Outpatient Veterans
S K OBOLER, A V PROCHAZKA, and T J MEYER

260 Animal Rights and Animal Experimentation—Implications for Physicians
A P GELPI

263 Durable Power of Attorney for Health Care—Are We Ready for It?
M K GOLDSTEIN, R P VALLONE, D C PASCOE, and C H WINOGRAD

269 Public Perceptions of Health Care Problems—An Analysis From Arizona
B L KIRKMAN-LIFF

CONFERENCES AND REVIEWS

274 Upper Gastrointestinal Tract Hemorrhage
Discussant: L LAINE

280 Primary Ciliary Dyskinesia
L LE MAUVIEL

EPITOMES

284 Important Advances in Emergency Medicine

ALERTS, NOTICES, AND CASE REPORTS

292 Severe Thyrotoxicosis Presenting as Acute Psychosis
T G CAUDILL and C K LARDINOIS

293 Cardiomyopathy Associated With High-Dose Interleukin-2 Therapy
A C BECK, J H WARD, E H HAMMOND, R B WRAY, and W E SAMLOWSKI

296 Idiopathic Mediastinitis With Superior Vena Cava Obstruction, Cardiac Tamponade, and Cutaneous Vasculitis
J M LOEB and C M LOMBARD

299 Home Treatment of Calf Deep Venous Thrombosis
C B CALLISTER, S D WOOD, G L WHITE Jr, and E D TUCKER

RADIOLOGIC CASE

301 A 3-Year-Old Boy With Neck Pain After Motor-Vehicle Accident
W ASLAMY, K DANIELSON, S J HESSEL, and J M LEVY

COMMENTARY

303 Partnerships for Improving Border Health
E O NIGHTINGALE and M G PECK

EDITORIALS

306 Border Health Spans the Continent • How We Get Stoned • Physicians and Animal Experimentation • International Health

LESSONS FROM THE PRACTICE

310 Desperately Seeking Primary Prevention
ANONYMOUS

OTHER FEATURES

214 Subscription Information

220 Continuing Medical Education Activities in Arizona; California, Hawaii, and Nevada; Colorado; Idaho; New Mexico; Utah; Washington; Wyoming

222 In Memoriam

242 Instructions for Authors

312 Poem

316 Classified Advertising

328 Western State Medical Associations' Meetings

Detailed Table of Contents: 219, 224, 228

Official Journal of the Alaska State Medical Association, the Arizona Medical Association, the California Medical Association, the Denver Medical Society, the Idaho Medical Association, the Nevada State Medical Association, the New Mexico Medical Society, the Utah Medical Association, the Washington State Medical Association, and the Wyoming Medical Society.

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- increased incidence of angina or new onset of angina

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Potential patients should have a history and physical and should be advised of potential risks. A risk/benefit decision should be made. Heart patients should realize that adverse effects may be especially serious.

Alert patients to the possibility of tachycardia and fluid retention and monitor for increased heart rate, weight gain, or other systemic effects.

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General Precautions: Monitor patients 1 month after starting ROGAINE and at least every 6 months afterward. Discontinue ROGAINE if systemic effects occur.

The alcohol base will burn and irritate the eye. If ROGAINE reaches sensitive surfaces (eg, eye, abraded skin, and mucous membranes), bathe with copious cool water.

Avoid inhaling the spray.

Do not use in conjunction with other topical agents such as corticosteroids, retinoids and petrolatum, or agents that enhance percutaneous absorption.

ROGAINE is for topical use only. Each mL contains 20 mg minoxidil and accidental ingestion could cause adverse systemic effects.

Decreased integrity of the epidermal barrier caused by inflammation or disease of the skin, eg, excoriations, psoriasis, or severe sunburn, may increase minoxidil absorption.

Patient Information: A patient information leaflet is included with each package and in the full product information.

Drug Interactions: No drug interactions are known. Theoretically, absorbed minoxidil may potentiate orthostatic hypotension in patients taking guanethidine.

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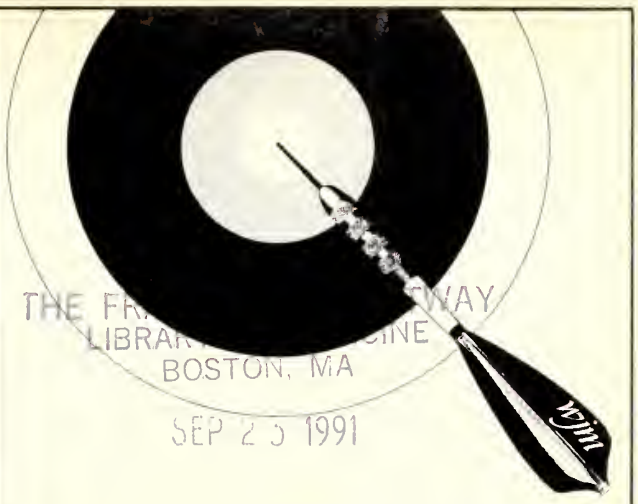

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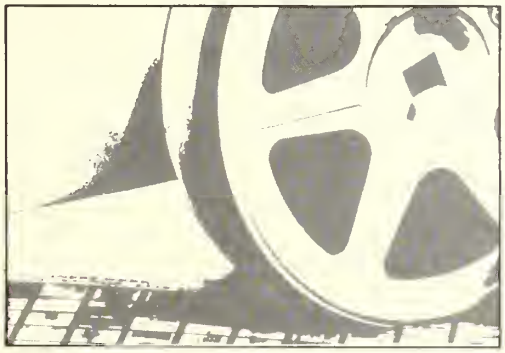

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1. A. Morales et al., New England Journal of Medicine 1221. November 12, 1981.
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CONTENTS

BIOMEDICAL SCIENCE

249 **Causes and Prevention of Calcium-containing Renal Calculi**

ROGER A. L. SUTTON, DM, FRCP, FRCPC

From the Department of Medicine, Division of Nephrology, University of British Columbia Faculty of Medicine, Vancouver.

ARTICLES

253 **Angiographic Yield in Penetrating Extremity Trauma**

VERNON HENDERSON, MD; RAMAN NAMBISAN, MD; MICHAEL E. SMITH, MD; KENNETH K. YIM, MD; and CLAUDE H. ORGAN, Jr, MD

From the Department of Surgery, University of California, Davis-East Bay, Oakland, California.

256 **Leg Symptoms in Outpatient Veterans**

SYLVIA K. OBOLER, MD; ALLAN V. PROCHAZKA, MD, MSc; and THOMAS J. MEYER, MD

From the Ambulatory Care Service, Veterans Affairs Medical Center, Denver, Colorado, and the Department of Medicine, University of Colorado Health Sciences Center, Denver.

260 **Animal Rights and Animal Experimentation—Implications for Physicians**

ARMAND P. GELPI, MD

From the Division of Extended Care, Veterans Administration Medical Center, Palo Alto, California.

263 **Durable Power of Attorney for Health Care—Are We Ready for It?**

MARY KANE GOLDSTEIN, MD; ROBERT P. VALLONE, PhD; DENNIS C. PASCOE, MSW; and CAROL HUTNER WINOGRAD, MD

From the Division of Endocrinology, Gerontology, and Metabolism, Stanford University Medical Center, Stanford, and the Geriatric Research, Education, and Clinical Center, Veterans Administration Medical Center, Palo Alto, California.

269 **Public Perceptions of Health Care Problems—An Analysis From Arizona**

BRADFORD L. KIRKMAN-LIFF, DrPH

From the School of Health Administration and Policy, College of Business, Arizona State University, Tempe.

CONFERENCES AND REVIEWS

274 **Upper Gastrointestinal Tract Hemorrhage**

Discussant: LOREN LAINE, MD

A discussion selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from a transcription, it has been edited by Nathan M. Bass, MD, PhD, Associate Professor of Medicine, under the direction of Lloyd H. Smith, Jr, MD, Professor of Medicine and Associate Dean in the School of Medicine.

280 **Primary Ciliary Dyskinesia**

LAURIE LE MAUVIEL, DO

From the College of Osteopathic Medicine of the Pacific, Pomona, California. This paper was chosen as the runner-up in THE WESTERN JOURNAL OF MEDICINE'*s 1991 Medical Student Writing Competition.*

EPITOMES—IMPORTANT ADVANCES IN CLINICAL MEDICINE

Emergency Medicine

Items of progress in emergency medicine. Each item, in the judgment of a panel of knowledgeable physicians, has recently became reasonably firmly established, both as to scientific fact and important clinical significance.

284 **Zidovudine for Prophylaxis of Human Immunodeficiency Virus Infection After Accidental Exposure**

LOUIS S. BINDER, MD, and JAMES A. CHAPPELL, MD

285 **Magnesium and Acute Myocardial Infarction**

CONNIE MITCHELL, MD

(Continued on Page 224)

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November 8-9—**Annual Southwestern Poison Symposium.** University of Arizona College of Medicine at Doubletree Hotel, Tucson. Fri-Sat. Contact: U of A.

November 8-9—**American College of Physicians, Arizona Chapter.** American College of Physicians at Ventana Canyon, Tucson. Fri-Sat. Contact: (800) 523-1546, ext 2723.

November 14-16—**Fourth Annual Spine Workshop.** Barrow's Neurological Institute, St Joseph's Hospital and Medical Center at Marriott's Mountain Shadows Resort, Scottsdale. Wed-Fri. Contact: Toby Anchie, (602) 285-3178 or (800) BARROW-1.

CONTACT INFORMATION

ArMA—Contact: Arizona Medical Association, 810 W. Bethany Home Rd, Phoenix, AZ 85013. (602) 246-8901.

Mayo Clinic-Scottsdale—Contact: Jodi Lee Smith, Postgraduate Courses, Mayo Clinic-Scottsdale, (602) 391-8300.

U of A—Contact: University of Arizona College of Medicine, Arizona Health Sciences Center, Tucson, AZ 85724. (602) 626-7832.

November 15-16—**Pediatric Genetics and Dermatology: A Practical Approach.** University of Arizona College of Medicine at Hotel Park Tucson. Fri-Sat. Contact: (602) 626-7832.

November 15-16—**4th Annual Techniques in Gynecological Surgery.** Mayo Clinic-Scottsdale at the Scottsdale Plaza Resort, Scottsdale. Fri-Sat. Contact: Trish Gean, Mayo Clinic-Scottsdale.

November 15-17—**The Advanced Medical Staff Seminar.** Joint Commission on the Accreditation of Health Care Organizations, Phoenix. Fri-Sun. Contact: Kyle Dooley Kinder, ArHA, (602) 968-1083.

November 22—**Update on Arthritis.** University of Arizona College of Medicine at the Sheraton Conquistador, Tucson. Fri. Contact: U of A.

November 24-27—**8th Annual "State of the Art in Total Joint Replacement."** Harrington Arthritis Research Center, St Luke's Hospital at the Scottsdale Princess Resort, Scottsdale. Sun-Wed. Contact: Nancy Neroni, (602) 254-0377.

CALIFORNIA, HAWAII, AND NEVADA

This listing of continuing education programs in California, Hawaii, and Nevada is supplied by the Committee on Continuing Medical Education of the California Medical Association. All courses and meetings listed have been approved for Category I credit toward the CMA Certificate in Continuing Medical Education. To have accredited courses listed here, please send information at least two months in advance to Department of Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690; or phone (415) 541-0900. For a list of organizations approved for Category I credit toward the CMA Certificate in Continuing Medical Education or for more information on accreditation or certification, please write to the above address.

ANESTHESIOLOGY

November 3-9—**Hawaiian Seminar on Clinical Anesthesia.** California Society of Anesthesiologists at Hyatt Regency Hotel, Poipu Beach, Kauai, Hawaii. 1 week. 20 hrs. $415. Contact: CSA, 1065 E Hillsdale Blvd, Ste 410, Foster City 94404. (800) 345-3691.

November 8-10—**Anesthesiology Update: 1991.** UCD at Monterey Plaza Hotel, Monterey. Fri-Sun. 14 hrs. $370. Contact: UCD.

January 19-21—**Second America-Japan Anesthesia Congress.** International Anesthesia Research Society at Sheraton Waikiki Hotel, Honolulu, Hawaii. Sun-Tue. 14 hrs. $250. Contact: Vicky Larsen, University of Utah School of Medicine, 50 North Medical Drive, Salt Lake City, UT 84132. (801) 581-6115.

January 19-24—**Hawaiian Seminar on Clinical Anesthesia.** California Society of Anesthesiologists at Westin Maui Hotel, Kaanapali Beach, Maui, Hawaii. Sun-Fri. 20 hrs. Contact: California Society of Anesthesiologists, 1065 E Hillsdale Blvd, #410, Foster City 94404. (800) 345-3691.

January 24-26—**30th Clinical Conference in Pediatric Anesthesiology.** Children's Hospital of Los Angeles at Stouffer Concourse Hotel. Fri-Sun. 15 hrs. Contact: Katherine Barky, MD, PO Box 54700, Los Angeles 90054. (213) 669-2262.

CARDIOLOGY

October 5—**Changing Perspectives in the Control of Ventricular Arrhythmias: Do We Make a Difference in Mortality?** UCLA at Beverly Hilton, Beverly Hills. Sat. 4 hrs. Contact: UCLA.

October 10-12—**Cardiology Update: 1991.** American College of Cardiology at Quail Lodge, Carmel. Thurs-Sat. 12.5 hrs. $440. Contact: ACC, Extramural Programs, Dept 5080, Washington, DC 20061-5080. (800) 253-4636.

October 18-19—**Coronary Heart Disease Update.** Medical Education Resources at Parc Fifty Hotel, San Francisco. Fri-Sat. Contact: Karen DeBont, MER, 1500 W Canal Ct, Ste 500, Littleton, CO 80120-4528. (800) 421-3756.

October 18-19—**Cardiology for the Clinician.** Memorial/UCI Center for Health Education. Fri-Sat. Contact: UCI.

(Continued on Page 236)

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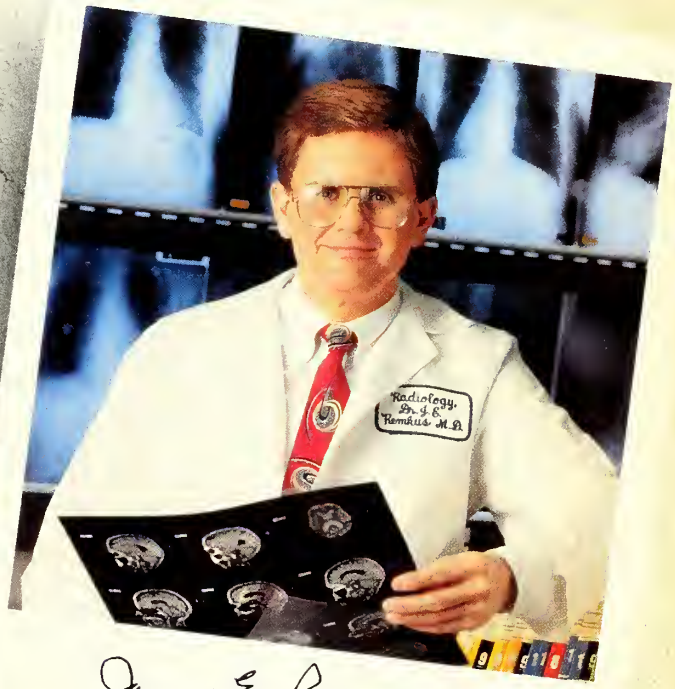

San Ramon Regional Medical Center, San Ramon, CA

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Applies to California residents only.

In Memoriam

California Medical Association

ADAMS, DEANE T., San Jose. Died Jun 30, 1991, aged 75. Graduate of University of Southern California, Los Angeles, 1942. Dr Adams was a member of the Santa Clara County Medical Association.

BERNER, RICHARD A., Santa Barbara. Died Jun 10, 1991, aged 60. Graduate of University of California, Los Angeles, School of Medicine, 1959. Licensed in California in 1960. Dr Berner was a member of the Santa Barbara County Medical Society.

CALLAHAN, ROSEMARIE, Fresno. Died Jun 13, 1991, aged 65. Graduate of Medical Faculty of Heidelberg, 1951. Dr Callahan was a member of the Fresno-Madera Medical Society.

CASBERG, MELVIN A., Solvang. Died Mar 27, 1991, aged 81. Graduate of St Louis University School of Medicine, St Louis, Missouri, 1936. Dr Casberg was a member of the Los Angeles County Medical Association.

CHENNELL, BRUCE A., Vallejo. Died Mar 30, 1991, aged 43. Graduate of McGill University Faculty of Medicine, Montreal, 1973. Licensed in California in 1974. Dr Chennell was a member of the Solano County Medical Society.

DRAPER, OLIVER D., Hemet. Died Apr 13, 1991, aged 79. Graduate of University of Oregon, Portland, 1940. Licensed in California in 1941. Dr Draper was a member of the San Diego County Medical Society.

FOLEY, ROBERT D., Fremont. Died Jun 8, 1991, aged 62. Graduate of University of New York, Buffalo, 1954. Licensed in California in 1959. Dr Foley was a member of the Alameda-Contra Costa Medical Association.

GERLACH, RICHARD D., Oakland. Died Jun 27, 1991, aged 62. Graduate of University of Chicago, 1955. Dr Gerlach was a member of the Alameda-Contra Costa Medical Association.

GOODSON, SAMUEL B., Monrovia. Died Jan 21, 1991, aged 76. Graduate of University of Illinois College of Medicine, Chicago, 1942. Licensed in California in 1946. Dr Goodson was a member of the Los Angeles County Medical Association.

GREENLAW, COLIN T., Sacramento. Died Jun 16, 1991, aged 77. Graduate of Loma Linda University School of Medicine, Loma Linda, California, 1949. Licensed in California in 1949. Dr Greenlaw was a member of the Sacramento-El Dorado Medical Society.

HACK, RUDOLF W., San Bernardino. Died Jul 10, 1991, aged 83. Graduate of University of Illinois College of Medicine, Chicago, 1935. Licensed in California in 1945. Dr Hack was a member of the San Bernardino County Medical Society.

JOHNSON, ALLEN R., Yreka. Died May 1, 1991, aged 57. Graduate of Loma Linda University School of Medicine, Loma Linda, California, 1959. Licensed in California in 1960. Dr Johnson was a member of the Siskiyou County Medical Society.

MASON, CHARLES E., Alhambra. Died Apr 9, 1991, aged 85. Graduate of Loma Linda University School of Medicine, Loma Linda, California, 1933. Licensed in California in 1933. Dr Mason was a member of the Los Angeles County Medical Association.

MOFFITT, LAURL W., San Diego. Died May 25, 1991, aged 85. Graduate of Baylor University, Houston, Texas, 1933. Licensed in California in 1935. Dr Moffitt was a member of the San Diego County Medical Society.

NUDELMAN, HOWARD LEE, Mountain View. Died Jul 1, 1991, aged 55. Graduate of Ohio State University, Columbus, 1960. Dr Nudelman was a member of the Santa Clara County Medical Association.

OLMSTEAD, LUKE R., Los Angeles. Died Feb 9, 1991, aged 34. Graduate of State University of New York, 1985. Licensed in California in 1986. Dr Olmstead was a member of the Los Angeles County Medical Association.

PAXSON, JANE T., Albany. Died May 1, 1991, aged 81. Graduate of University of Wisconsin Medical School, Madison, 1932. Dr Paxson was a member of the Alameda-Contra Costa Medical Association.

ROBLEY, WENDELL W., Spring Valley. Died May 21, 1991, aged 88. Graduate of Northwestern University, Chicago, Illinois, 1943. Dr Robley was a member of the San Diego County Medical Society.

RUBENS, MARK KENNETH, San Diego. Died May 1991, aged 36. Graduate of University of Michigan, 1981. Dr Rubens was a member of the San Diego County Medical Society.

SCHMELA, WOODROW W., Ventura. Died May 28, 1991, aged 77. Dr Schmela was a member of the Ventura County Medical Society.

SPLITHOFF, CLARENCE A., Oakland. Died Jun 17, 1991, aged 81. Graduate of Northwestern University Medical School, Chicago, Illinois, 1933. Dr Splithoff was a member of the Alameda-Contra Costa Medical Association.

WALDRON, MELVIN C. Died Jan 13, 1991, aged 71. Graduate of Loma Linda University School of Medicine, Loma Linda, California, 1952. Licensed in California in 1952. Dr Waldron was a member of the Riverside County Medical Association.

WEILER, PHILIP G., Davis. Died Jun 14, 1991, aged 50. Graduate of Tulane University School of Medicine, New Orleans, Louisiana, 1965. Licensed in California in 1979. Dr Weiler was a member of the Sacramento-El Dorado Medical Society.

WHITE, EDWARD D., Alameda. Died Jun 2, 1991, aged 70. Graduate of University of California, San Francisco, 1944. Dr White was a member of the Alameda-Contra Costa Medical Association.

Denver Medical Society

MUSMAN, DAVID J. Died Jun 17, 1991, aged 78. Graduate of University of Colorado Medical School, 1937. Licensed in Colorado in 1937.

New Mexico Medical Society

BLAKE, HENRY W., Albuquerque. Died Jun 23, 1991, aged 58. Graduate of University of Louvain, Belgium, 1953. Licensed in New Mexico in 1955. Dr Blake was a member of the Greater Albuquerque Medical Association.

FARID, SADA, Albuquerque. Died Mar 1991, aged 66. Graduate of Faculte de Medecine d'Haiti, 1956. Licensed in New Mexico in 1963. Dr Farid was a member of the Greater Albuquerque Medical Association.

SMITH, GEORGE L., Albuquerque. Died Jun 12, 1991, aged 62. Graduate of Boston School of Medicine, Massachusetts, 1955. Licensed in New Mexico in 1962. Dr Smith was a member of the Luna Hidalgo County Medical Society.

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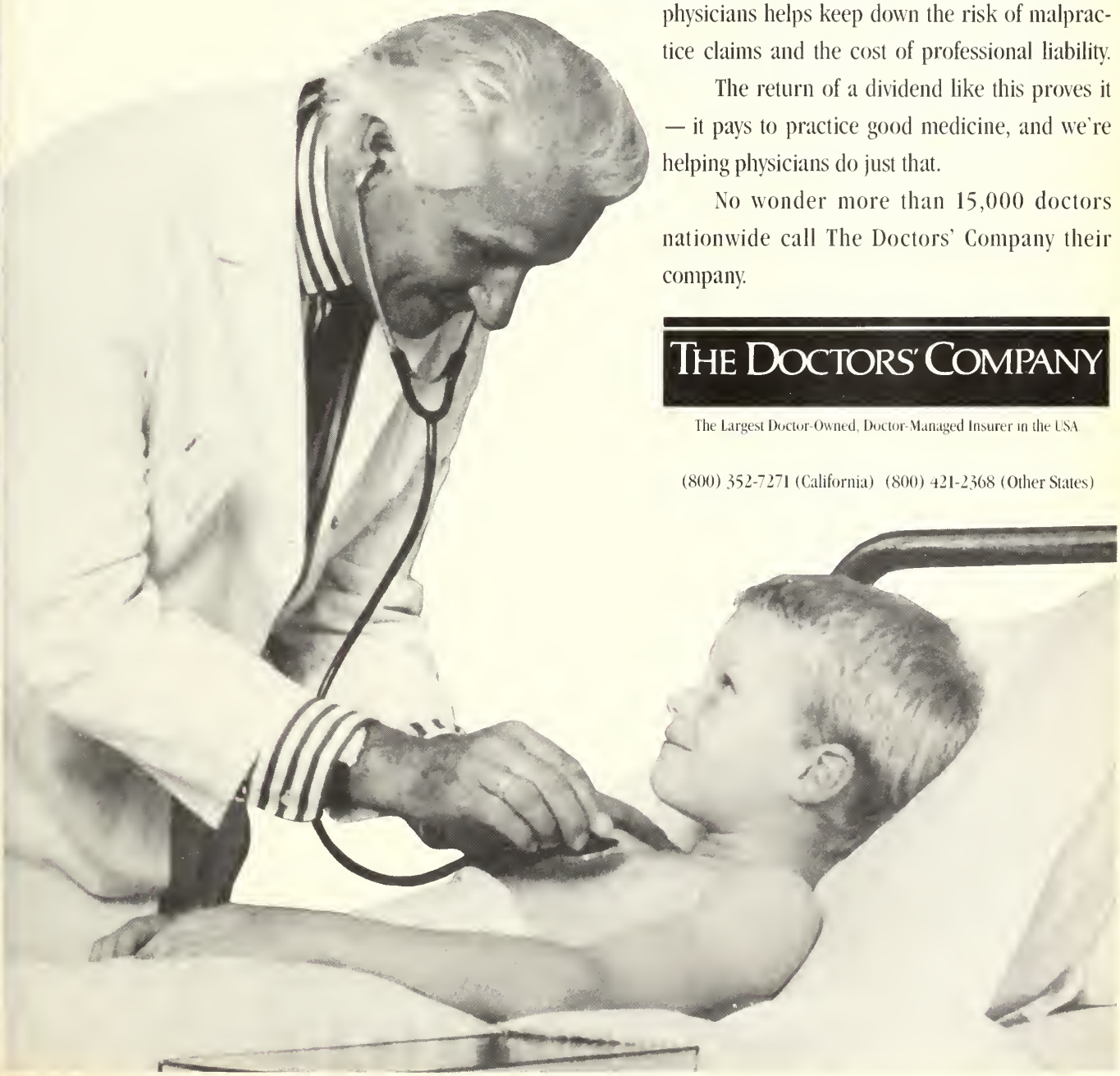

(Continued from Page 219)

285 **Preventing and Controlling Violence in Emergency Departments**
GREGG A. PANE, MD, MPA

286 **Neuromuscular Blockage in Emergency Medicine**
EDWARD A. PANACEK, MD

287 **Transvaginal Imaging of Ectopic Pregnancy**
MICHAEL CRADE, MD

287 **Rectal Diazepam Therapy for Prehospital Pediatric Status Epilepticus**
RONALD A. DIECKMANN, MD

288 **Bacterial Meningitis in Emergency Departments**
ERIC WEISS, MD

289 **Human Immunodeficiency Virus Precautions in Emergency Departments**
ALAN GELB, MD

289 **High-Dose Epinephrine in Cardiac Arrest**
MICHAEL CALLAHAM, MD

290 **When to Image Cervical Spine Injuries**
JEROME R. HOFFMAN, MD, and WILLIAM MOWER, MD

290 **Terminating Paroxysmal Supraventricular Tachycardias With Adenosine**
JULIA NATHAN, MD

ALERTS, NOTICES, AND CASE REPORTS

292 **Severe Thyrotoxicosis Presenting as Acute Psychosis**
TIMOTHY G. CAUDILL, MD, and CLAUDE K. LARDINOIS, MD

From the Department of Medicine, Division of Physiology, University of Nevada School of Medicine, and the Department of Medicine, Division of Endocrinology, Veterans Affairs Medical Center, Reno, Nevada.

293 **Cardiomyopathy Associated With High-Dose Interleukin-2 Therapy**
ANNA C. BECK, MD; JOHN H. WARD, MD; ELIZABETH H. HAMMOND, MD; ROBERT B. WRAY, MD; and WOLFRAM E. SAMLOWSKI, MD

From the Department of Internal Medicine, University of Utah-Veterans Affairs Medical Center Cancer Immunotherapy Program, and the Department of Pathology, University of Utah School of Medicine; the Department of Pathology, LDS Hospital, and the Department of Veterans Affairs Medical Center, Salt Lake City, Utah.

296 **Idiopathic Mediastinitis With Superior Vena Cava Obstruction, Cardiac Tamponade, and Cutaneous Vasculitis**
JOHN M. LOEB, MD, and CHARLES M. LOMBARD, MD

From the Eden Medical Center, Castro Valley, and the Pathology Department, El Camino Hospital, Mountain View, California.

299 **Home Treatment of Calf Deep Venous Thrombosis**
CYRIL BRUCE CALLISTER, PA-C; STEPHEN DANIEL WOOD, MD, MSPH; GEORGE L. WHITE, Jr, PA-C, PhD, MSPH; and ELIZABETH D. TUCKER, RN

From the Foothill Family Clinic; the Physician's Assistant Program, Departments of Family and Preventive Medicine and Ophthalmology, University of Utah School of Medicine; and the New England Critical Care Company, Salt Lake City, Utah. Dr White is currently with the Center for Community Health, Department of Health Education, College of Health and Human Sciences, University of Southern Mississippi, Hattiesburg.

RADIOLOGIC CASE

301 **A 3-Year-Old Boy With Neck Pain After Motor-Vehicle Accident**
WAZHMA ASLAMY; KELVIN DANIELSON, MD; SAMUEL J. HESSEL, MD; and JONATHAN M. LEVY, MD

Ms Aslamy is a fourth-year medical student at the University of Arizona School of Medicine, Tucson. From the Department of Diagnostic Radiology, Scottsdale Memorial Hospital, Scottsdale, Arizona.

(Continued on Page 228)

NOW ON MEDI-CAL

Treat hypertension at its source with...

ONCE-A-DAY

CARDURA®

(doxazosin mesylate) Scored Tablets 1 mg, 2 mg, 4 mg, 8 mg

CARDURA is well tolerated. Only three common side effects were different from placebo: dizziness, somnolence, and fatigue. These were generally mild and transient; only 2% of patients in placebo-controlled studies discontinued due to adverse effects—the same rate as placebo. Syncope has been reported, but rarely (< 1%).

Please see brief summary of prescribing information on adjacent page of this advertisement.

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ONCE-A-DAY

CARDURA®

(doxazosin mesylate) Scored Tablets 1 mg, 2 mg, 4 mg, 8 mg

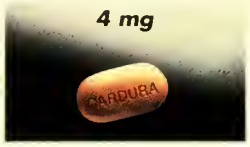
Convenient once-a-day dosage

Most responsive patients are controlled with one daily dose of 4 to 8 mg[1]

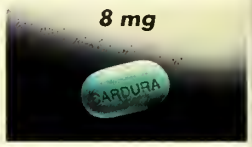
—recommended initial dose is 1 mg, with dosage range of 1 mg to 16 mg per day.

1 ***Begin all patients with CARDURA 1 mg once daily to minimize side effects. Evaluate supine and standing blood pressure. Prescribe CARDURA 2 mg once daily, if necessary.***

2 ***Evaluate for blood pressure control. Prescribe 4 mg once daily, if necessary.***



3 ***Evaluate for blood pressure control. Prescribe 8 mg once daily, if necessary. Maximum recommended dosage is 16 mg once daily.***



Reference: 1. Data available on request from Roerig

CAROURA® (doxazosin mesylate) Tablets

Briot Summary ot Prescribing Information

INDICATIONS AND USAGE

CARDURA (doxazosin mesylate) is indicated for the treatment of hypertension. CARDURA may be used alone or in combination with diuretics or beta-adrenergic blocking agents There is limited experience with CARDURA in combination with angiotensin converting enzyme inhibitors or calcium channel blockers

CDNTRAINDICATIDNS

CARDURA is contraindicated in patients with a known sensitivity to quinazolines (e.g prazosin, terazosin)

WARNINGS

Syncope and "First-dose" Effect:

Doxazosin, like other alpha-adrenergic blocking agents, can cause marked hypotension, especially in the upright position, with syncope and other postural symptoms such as dizziness. Marked orthostatic effects are most common with the first dose but can also occur when there is a dosage increase, or it therapy is interrupted tor more than a tew days. To decrease the likelihood ot excessive hypotension and syncope, it is essential that treatment be initiated with the 1 mg dose. The 2, 4, and 8 mg tablets are not tor initial therapy. Dosage should then be adjusted slowly (see OOSAGE AND ADMINISTRATIDN section) with increases in dose every two weeks. Additional antihypertensive agents should be added with caution.

Patients being titrated with doxazosin should be cautioned to avoid situations where injury could result should syncope occur.

In an early investigatonal study of the safety and tolerance of increasing daily doses of doxazosin in normotensives beginning at 1 mg/day, only 2 of 6 subjects could tolerate more than 2 mg/day without experiencing symptomatic postural hypotension In another study of 24 healthy normotensive male subjects receiving initial doses of 2 mg/day ot doxazosin, seven (29%) ot the subjects experienced symptomatic postural hypotension between 0 5 and 6 hours after the first dose necessitating termination ot the study In this study 2 of the normotensive subjects experienced syncope Subsequent trials in hypertensive patients always began doxazosin dosing at 1 mg/day resulting in a 4% incidence of postural side effects at 1 mg/day with no cases of syncope

In multiple dose clinical trials involving over 1500 patients with dose titration every one to two weeks, syncope was reported in 0 7% of patients None of these events occurred at the starting dose of 1 mg and 1 2% (8/664) occurred at 16 mg/day

It syncope occurs, the patient should be placed in a recumbent position and treated supportively as necessary.

PRECAUTIDNS

General:

1. Orthostatic Hypotension:

While syncope is the most severe orthostatic effect of CARDURA, other symptoms of fowered blood pressure, such as dizziness, lightheadedness, or vertigo, can occur, especially at initiation of therapy or at the time of dose increases These were common in clinical trials, occurring in up to 23% of all patients treated and causing discontinuation of therapy in about 2%

In placebo controlled titration trials orthostatic effects were minimized by beginning therapy at 1 mg per day and titrating every two weeks to 2, 4, or 8 mg per day There was an increased frequency of orthostatic effects in patients given 8 mg or more, 10%, compared to 5% at 1-4 mg and 3% in the placebo group

Patients in occupations in which orthostatic hypotension could be dangerous should be treated with particular caution

If hypotension occurs, the patient should be placed in the supine position and, if this measure is inadequate, volume expansion with intravenous fluids or vasopressor therapy may be used A transient hypotensive response is not a contraindication to further doses ot CARDURA

2. Impaired liver function:

CARDURA should be administered with caution to patients with evidence ot impaired hepatic function or to patients receiving drugs known to influence hepatic metabolism (see CLINICAL PHARMACDLDGY). There is no controlled clinical experience with CARDURA in patients with these conditions

3. Leukopenia/Neutropenia:

Analysis of hematologic data from patients receiving CARDURA in controlled clinical trials showed that the mean W8C (N=474) and mean neutrophil counts (N=419) were decreased by 2 4% and 1 0% respectively, compared to placebo, a phenomenon seen with other alpha blocking drugs A search through a data base of 2400 patients revealed 4 in which drug-related neutropenia could not be ruled out Two had a single low value on the last day of treatment Two had stable, non-progressive neutrophil counts in the 1000/mm^3 range over periods of 20 and 40 weeks In cases where follow-up was available the W8Cs and neutrophil counts returned to normal after discontinuation ol CARDURA No patients became symptomatic as a result of the low WBC or neutrophil counts.

Information for Patients:

Patients should be made aware of the possibility of syncopal and orthostatic symptoms, especially at the initiation ot therapy, and urged to avoid driving or hazardous tasks for 24 hours after the first dose, after a dosage increase, and after interruption of therapy when treatment is resumed They should be cautioned to avoid situations where injury could result should syncope occur during initiation ot doxazosin therapy They should also be advised of the need to sit or lie down when symptoms ol lowered blood pressure occur, although these symptoms are not always orthostatic, and to be careful when rising from a sitting or lying position If dizziness, lightheadedness, or palpitations are bothersome they should be reported to the physician, so that dose adjustment can be considered Patients should also be told that drowsiness or somnolence can occur with doxazosin, requiring caution in people who must drive or operate heavy machinery

Drug Interactions:

Most (98%) of plasma doxazosin is protein bound *In vitro* data in human plasma indicate that CARDURA has no effect on protein binding of digoxin, wartarin, phenytoin or indomethacin There is no information on the effect of other highly plasma protein bound drugs on doxazosin binding CAROURA has been administered without any evidence of an adverse drug interaction to patients receiving thiazide diuretics, beta blocking agents, and nonsteroidal anti-inflammatory drugs.

Orug/Laboratory test interactions:

None known

Cardiac Toxicity in Animals:

An increased incidence of myocardial necrosis or fibrosis was displayed by Sprague-Dawley rats after 6 months of dietary administration at concentrations calculated to provide 80 mg doxazosin/kg/day and after 12 months of dietary administration at concentrations calculated to provide 40 mg doxazosin/kg/day (150 times the maximum recommended human dose assuming a patient weight of 60 kg). There is no evidence that similar lesions occur in humans

Carcinogenesis, Mutagenesis and Impairment ot Fertility:

Chronic dietary administration (up to 24 months) of doxazosin mesylate at maximally tolerated concentrations (highest dose 40 mg/kg about 150 times the maximum recommended human dose of 16 mg/60 kg) revealed no evidence of carcinogenicity in rats. There was also no evidence of carcinogenicity in a similarly conducted study (up to 18 months of dietary administration) in mice The mouse study, however, was compromised by the failure to use a maximally tolerated dose of doxazosin

Mutagenicity studies revealed no drug- or metabolite-related effects at either chromosomal or subchromosomal levels.

Studies in rats showed reduced fertility in males treated with doxazosin at oral doses of 20 (but not 5 or 10) mg/kg/day, about 75 times the maximum recommended human dose This effect was reversible within two weeks of drug withdrawal.

Pregnancy

Teratogenic Effects, Pregnancy Category B. Studies in rabbits and rats at daily oral doses of up to 40 and 20 mg/kg, respectively (150 and 75 times the maximum recommended daily dose of 16 mg, assuming a patient weight of 60 kg), have revealed no evidence ol harm to the fetus The rabbit study, however, was compromised by the failure to use a maximally tolerated dose of doxazosin There are no adequate and well-controlled studies in pregnant women 8ecause animal reproduction studies are not always predictive of human response, CARDURA should be used during pregnancy only il clearly needed

Radioactivity was found to cross the placenta following oral administration of labelled doxazosin to pregnant rats.

Nonteratogenic Effects. In peri-postnatal studies in rats, postnatal development at maternal doses of 40 or 50 mg/kg/day ol doxazosin was delayed as evidenced by slower body weight gain and a slightly later appearance ol anatomical features and reflexes.

Nursing Mothers

It is not known whether this drug is excreted in human milk 8ecause many drugs are excreted in human milk, caution should be exercised when CARDURA is administered to a nursing mother

Pediatric Use

Safety and effectiveness in children have not been established

ADVERSE REACTIONS

CARDURA has been administered to approximately 4000 patients, of whom 1679 were included in the clinical development program In that program, minor adverse effects were frequent, bul led to discontinuation of treatment in only 7% of patients In placebo-controlled studies adverse effects occurred in 49% and 40% of patients in the doxazosin and placebo groups, respectively, and led to discontinuation in 2% of patients in each group The major reasons lor discontinuation were postural effects (2%), edema, malaise/fatigue, and some heart rate disturbance, each about 0 7%

In controlled clinical trials directly comparing CARDURA to placebo there was no significant difference in the incidence of side effects, except for dizziness (including postural), weight gain, somnolence and fatigue/malaise Postural effects and edema appeared to be dose related.

The prevalence rates presented below are based on combined data from placebo-controlled studies involving once daily administration of doxazosin at doses ranging from 1-16 mg Table 1 summarizes those adverse experiences (possibly/probably related) reported for patients in these studies where the prevalence rate in the doxazosin group was at feast 0 5% or where the reaction is of particular interest

TABLE 1. ADVERSE REACTIONS DURING PLACE8O CONTROLLEO STUOIES

		DOXAZOSIN (N=339)	PLACE8D (N=336)
CARDIOVASCULAR	Dizziness	19%	9%
	Vertigo	2%	1%
	Postural Hypotension	0 3%	0%
	Edema	4%	3%
	Palpitation	2%	3%
	Arrhythmia	1%	0%
	Hypotension	1%	0%
	Tachycardia	0 3%	1%
	Peripheral Ischemia	0 3%	0%
SKIN APPENDAGES	Rash	1%	1%
	Pruritus	1%	1%
MUSCULOSKELETAL	Arthralgia/Arthritis	1%	0%
	Muscle Weakness	1%	0%
	Myalgia	1%	0%
CENTRAL & PERIPHERAL N.S.	Headache	14%	16%
	Paresthesia	1%	1%
	Kinetic Oisorders	1%	0%
	Ataxia	1%	0%
	Hypertonia	1%	0%
	Muscle Cramps	1%	0%
AUTONOMIC	Mouth Dry	2%	2%
	Flushing	1%	0%
SPECIAL SENSES	Vision Abnormal	2%	1%
	Conjunctivitis/Eye Pain	1%	1%
	Tinnitus	1%	0 3%
PSYCHIATRIC	Somnolence	5%	1%
	Nervousness	2%	2%
	Depression	1%	1%
	Insomnia	1%	1%
	Sexual Dysfunction	2%	1%
GASTRDINTESTINAL	Nausea	3%	4%
	Diarrhea	2%	3%
	Constipation	1%	1%
	Dyspepsia	1%	1%
	Flatulence	1%	1%
	Abdominal Pain	0%	2%
	Vomiting	0%	1%
RESPIRATORY	Rhinitis	3%	1%
	Dyspnea	1%	1%
	Epistaxis	1%	0%
URINARY	Polyuria	2%	0%
	Urinary Incontinence	1%	0%
	Micturation Frequency	0%	2%
GENERAL	Fatigue/Malaise	12%	6%
	Chest Pain	2%	2%
	Asthenia	1%	1%
	Face Edema	1%	0%
	Pain	2%	2%

Additional adverse reactions have been reported, but these are, in general, not distinguishable from symptoms that might have occurred in the absence of exposure to doxazosin The lolfowing adverse reactions occurred with a frequency of between 0 5% and 1% syncope, hypoesthesia, increased sweating, agitation, increased weight The lollowing additional adverse reactions were reported by <0.5% of 3960 patients who received doxazosin in controlled or open, short- or long-term clinical studies, including international studies *Cardiovascular System*: angina pectoris, myocardial infarction, cerebrovascular accident, *Autonomic Nervous System*: pallor, *Metabolic*: thirst, gout, hypokalemia; *Hematopoietic*: lymphadenopathy, purpura, *Reproductive System*: breast pain, *Skin Disorders*: alopecia, dry skin, eczema, *Central Nervous System*: paresis, tremor, twitching, confusion, migraine, impaired concentration, *Psychiatric*: paroniria, amnesia, emotional lability, abnormal thinking, depersonalization, *Special Senses*: parosmia, earache, taste perversion, photophobia, abnormal lacrimation, *Gastrointestinal System*: increased appetite, anorexia, fecal incontinence, gastroenteritis; *Respiratory System*: bronchospasm, sinusitis, coughing, pharyngitis, *Urinary System*: renal calculus; *General Body System*: hot flashes, back pain, infection, fever/rigors, decreased weight, influenza-like symptoms.

CARDURA has not been associated with any clinically significant changes in routine biochemical tests No clinically relevant adverse effects were noted on serum potassium, serum glucose, uric acid, blood urea nitrogen, creatinine or liver function tests CARDURA has been associated with decreases in white blood cell counts (See Precautions)

OVERDDSAGE

The oral LD_{50} of doxazosin is greater than 1000 mg/kg in mice and rats The most likely manifestation of overdosage would be hypotension, for which the usual treatment would be intravenous infusion of fluid As doxazosin is highly protein bound, dialysis would not be indicated

OOSAGE AND ADMINISTRATION

DOSAGE MUST BE INDIVIOUALIZED. The initial dosage of CARDURA in hypertensive patients is 1 mg given once daily. Depending on the individual patient's standing blood pressure response (based on measurements taken at 2-6 hours postdose and 24 hours postdose), dosage may then be increased to 2 mg and thereafter if necessary to 4 mg, 8 mg and 16 mg to achieve the desired reduction in blood pressure. Increases in dose beyond 4 mg increase the likelihood of excessive postural effects including syncope, postural dizziness/vertigo, postural hypotension At a titrated dose of 16 mg once daily the frequency of postural effects is about 12% compared to 3% for placebo.

HOW SUPPLIED

CARDURA (doxazosin mesylate) is available as colored tablets for oral administration Each tablet contains doxazosin mesylate equivalent to 1 mg (white), 2 mg (yellow), 4 mg (orange) or 8 mg (green) of the active constituent, doxazosin

CARDURA® TA8LETS are available as 1 mg (white), 2 mg (yellow), 4 mg (orange) and 8 mg (green) scored tablets 8ottles of 100. 1 mg (NDC 0049-2750-66), 2 mg (NDC 0049-2760-66), 4 mg (NDC 0049-2770-66), 8 mg (NOC 0049-2780-66)

Recommended Storage Store below 86°F(30°C).

CAUTION: Federal law prohibits dispensing without prescription.

65-4538-00-0 Issued Nov 1990

Pfizer Roerig

A division of Pfizer Pharmaceuticals

ABSTRACTS SEPTEMBER 1991

(Henderson V, Nambisan R, Smith ME, Yim KK, Organ CH Jr: Angiographic yield in penetrating extremity trauma. West J Med 1991 Sep; 155:253-255)

Indications for angiography in the evaluation of penetrating extremity trauma remain controversial. Our experience was reviewed to determine the yield of angiography in penetrating extremity trauma and to correlate clinical findings with angiographic results. During an 81-month period from 1983 through 1989, 284 extremity arteriograms were carried out in 268 patients. The angiographic yield in patients with abnormal clinical findings was 51%. The angiographic yield in patients when proximity of the injury to major vessels was the only indication was 6% (7% with gunshot wounds and 0% with stab wounds). Neurologic deficit alone as an indication for angiography accounted for 55% of the angiograms interpreted as "negative" and none of those interpreted as "positive." We conclude that the use of angiography in patients with gunshot wounds to the extremity with "proximity injuries" to major vessels should continue, its use is not warranted in extremity stab wounds when proximity is the sole indication, and abnormal neurologic findings in the absence of other findings are a poor predictor of vascular injury.

ANGIOGRAPHY
TRAUMA
PENETRATING EXTREMITY TRAUMA
VASCULAR INJURIES

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ANGIOGRAPHY
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PENETRATING EXTREMITY TRAUMA
VASCULAR INJURIES

Three copies of this abstract are provided to help you in filing and cross-referencing research articles.

(Continued from Page 224)

COMMENTARY

303 **Partnerships for Improving Border Health**
ELENA O. NIGHTINGALE, MD, PhD, and MAGDA G. PECK, ScD, PA
From the Carnegie Corporation of New York, New York, and the Department of Pediatrics, University of Nebraska Medical Center, Omaha.

EDITORIALS

306 **Border Health Spans the Continent**

306 **How We Get Stoned**

307 **Physicians and Animal Experimentation**
THOMAS A. RAFFIN, MD
From the Division of Pulmonary and Critical Care Medicine, Stanford University Medical Center, and the Stanford University Center for Biomedical Ethics, Stanford, California.

308 **International Health**
ANVAR VELJI, MD
From the University of California, Davis, Medical Center, and the Kaiser Permanente Medical Center, Sacramento, California.

LESSONS FROM THE PRACTICE

310 **Desperately Seeking Primary Prevention**
ANONYMOUS

OTHER FEATURES

214 **Subscription Information**

220 **Continuing Medical Education Activities in Arizona; California, Hawaii, and Nevada; Colorado; Idaho; New Mexico; Utah; Washington; Wyoming**

222 **In Memoriam**

242 **Instructions for Authors**

312 **Poem**

316 **Classified Advertising**

328 **Western State Medical Associations' Meetings**

★ Official Journal of the Alaska State Medical Association, the Arizona Medical Association, the California Medical Association, the Denver Medical Society, the Idaho Medical Association, the Nevada State Medical Association, the New Mexico Medical Society, the Utah Medical Association, the Washington State Medical Association, and the Wyoming Medical Society.

★ Affiliated Clinical Investigation Societies: the Western Association of Physicians; the Western Society for Clinical Investigation; the Western Section, American Federation for Clinical Research; the Western Society for Pediatric Research; the Western Region, Society for Investigative Dermatology.

The EXCEL Study:
48 weeks, 8,245 patients,
362 medical centers,
in the largest-ever U.S.
randomized, double-blind,
placebo-controlled
trial of patients with primary
hypercholesterolemia

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the results are in...

For a Brief Summary of Prescribing Information,
please see the last page of this advertisement.

Bradford, R.H. et al.: Expanded clinical evaluation of lovastatin (EXCEL) study results: I. Efficacy in modifying plasma lipoproteins and adverse event profile in 8,245 patients with moderate hypercholesterolemia, *Archives of Internal Medicine,* January 1991.

Lovastatin lowere
Lovastatin lowere
Lovastatin lowere
Lovastatin raised

MEVACOR® (Lovastatin, MSD) is contraindicated in patients who are hypersensitive to any component of the medication; in patients with active liver disease or unexplained persistent transaminase elevations; in pregnant or lactating patients; and in women of childbearing age, except when such patients are highly unlikely to conceive.

For complete details on MEVACOR, including cautionary information regarding myopathy, drug interactions, liver enzyme monitoring, and slit-lamp monitoring, please refer to the Prescribing Information.

For a Brief Summary of Prescribing Information, please see the last page of this advertisement.

*Mean percent changes from baseline (n=6,582)
**Triglyceride values are median changes.
Dosage ranged from 20 mg q.p.m. to 40 mg b.i.d.

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DL cholesterol* 24-40%

otal cholesterol* 17-29%

iglycerides** 10-19%

DL cholesterol* 6.6-9.5%

For many patients with primary hypercholesterolemia (Types IIa and IIb), when diet and other nondrug therapies are inadequate

MEVACOR®

(LOVASTATIN | MSD)

Tablets, 20 mg 40 mg

MSD
MERCK SHARP & DOHME

MEVACOR®
(LOVASTATIN | MSD)

CONTRAINDICATIONS: Hypersensitivity to any component of this medication.

Active liver disease or unexplained persistent elevations of serum transaminases.

Pregnancy and lactation.

Atherosclerosis is a chronic process and the discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. Moreover, cholesterol and other products of the cholesterol biosynthesis pathway are essential components for fetal development, including synthesis of steroids and cell membranes. Because of the ability of inhibitors of HMG-CoA reductase such as MEVACOR® (Lovastatin, MSD) to decrease the synthesis of cholesterol and possibly other products of the cholesterol biosynthesis pathway, MEVACOR may cause fetal harm when administered to a pregnant woman. Therefore, lovastatin is contraindicated during pregnancy. Lovastatin should be administered to women of childbearing age only when such patients are highly unlikely to conceive. If the patient becomes pregnant while taking this drug, lovastatin should be discontinued and the patient should be apprised of the potential hazard to the fetus.

WARNINGS: ***Liver Dysfunction*. Marked persistent increases (to more than 3 times the upper limit of normal) in serum transaminases occurred in 1.9% of adult patients who received lovastatin for at least one year in clinical trials (see ADVERSE REACTIONS).** When the drug was interrupted or discontinued in these patients, the transaminase levels usually fell slowly to pretreatment levels. The increases usually appeared 3 to 12 months after the start of therapy with lovastatin and were not associated with jaundice or other clinical signs or symptoms. There was no evidence of hypersensitivity. A liver biopsy was done in one of these patients and showed areas of focal hepatitis. In this patient, transaminase levels returned to normal following discontinuation of therapy. Some of these patients had abnormal liver function tests prior to lovastatin therapy and/or consumed substantial quantities of alcohol.

It is recommended that liver function tests be performed before treatment begins, every 4 to 6 weeks during the first 15 months of therapy with lovastatin, and periodically thereafter in all patients. Special attention should be paid to patients who develop elevated serum transaminase levels, and in these patients, measurements should be repeated promptly and then performed more frequently. If the transaminase levels show evidence of progression, particularly if they rise to 3 times the upper limit of normal and are persistent, the drug should be discontinued. Liver biopsy should be considered if elevations are persistent beyond the discontinuation of the drug.

The drug should be used with caution in patients who consume substantial quantities of alcohol and/or have a past history of liver disease. Active liver disease or unexplained transaminase elevations are contraindications to the use of lovastatin.

As with other lipid-lowering agents, moderate (less than 3 times the upper limit of normal) elevations of serum transaminases have been reported following therapy with MEVACOR (see ADVERSE REACTIONS). These changes appeared soon after initiation of therapy with MEVACOR, were often transient, were not accompanied by any symptoms, and interruption of treatment was not required.

***Skeletal Muscle*: Rhabdomyolysis has been associated with lovastatin therapy alone, when combined with immunosuppressive therapy including cyclosporine in cardiac transplant patients, and when combined in non-transplant patients with either gemfibrozil or lipid-lowering doses (≥ 1 g day) of nicotinic acid. Some of the affected patients had preexisting renal insufficiency, usually as a consequence of long-standing diabetes. Acute renal failure from rhabdomyolysis has been seen more commonly with the lovastatin-gemfibrozil combination and has also been reported in transplant patients receiving lovastatin plus cyclosporine.**

Rhabdomyolysis with or without renal impairment has been reported in seriously ill patients receiving erythromycin concomitantly with lovastatin. Therefore, patients receiving concomitant lovastatin and erythromycin should be carefully monitored.

Fulminant rhabdomyolysis has been seen as early as 3 weeks after initiation of combined therapy with gemfibrozil and lovastatin but may be seen after several months. For these reasons, it is felt that, in most subjects who have had an unsatisfactory lipid response to either drug alone, the possible benefits of combined therapy with lovastatin and gemfibrozil do not outweigh the risks of severe myopathy, rhabdomyolysis, and acute renal failure. While it is not known whether this interaction occurs with fibrates other than gemfibrozil, myopathy and rhabdomyolysis have occasionally been associated with the use of other fibrates alone, including clofibrate. Therefore, the combined use of lovastatin with other fibrates should generally be avoided.

Physicians contemplating combined therapy with lovastatin and lipid-lowering doses of nicotinic acid or with immunosuppressive drugs should carefully weigh the potential benefits and risks and should carefully monitor patients for any signs and symptoms of muscle pain, tenderness, or weakness, particularly during the initial months of therapy and during any periods of upward dosage titration of either drug. Periodic CPK determinations may be considered in such situations, but there is no assurance that such monitoring will prevent the occurrence of severe myopathy. The monitoring of lovastatin drug and metabolite levels may be considered in transplant patients who are treated with immunosuppressives and lovastatin.

Lovastatin therapy should be temporarily withheld or discontinued in any patient with an acute, serious condition suggestive of a myopathy or having a risk factor predisposing to the development of renal failure secondary to rhabdomyolysis, including severe acute infection, hypotension, major surgery, trauma, severe metabolic, endocrine, and electrolyte disorders, and uncontrolled seizures.

Myalgia has been associated with lovastatin therapy. Transient, mildly elevated creatine phosphokinase levels are commonly seen in lovastatin-treated patients. However, in clinical trials, approximately 0.5% of patients developed a myopathy, i.e., myalgia or muscle weakness associated with markedly elevated CPK levels. Myopathy should be considered in any patient with diffuse myalgias, muscle tenderness, or weakness, and/or marked elevation of CPK. Patients should be advised to report promptly unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever. Lovastatin therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected.

Most of the patients who have developed myopathy (including rhabdomyolysis) while taking lovastatin were receiving concomitant therapy with immunosuppressive drugs, gemfibrozil, or lipid-lowering doses of nicotinic acid. In clinical trials, about 30% of patients on concomitant immunosuppressive therapy including cyclosporine developed myopathy, the corresponding percentages for gemfibrozil and niacin were approximately 5% and 2%, respectively.

In 6 patients with cardiac transplants taking immunosuppressive therapy including cyclosporine concomitantly with lovastatin 20 mg/day, the average plasma level of active metabolites derived from lovastatin was elevated to approximately 4 times the expected levels. Because of an apparent relationship between increased plasma levels of active metabolites derived from lovastatin and myopathy, the daily dosage in patients taking immunosuppressants should not exceed 20 mg/day (see DOSAGE AND ADMINISTRATION). Even at this dosage, the benefits and risks of using lovastatin in patients taking immunosuppressants should be carefully considered.

PRECAUTIONS: ***General***: Before instituting therapy with MEVACOR, an attempt should be made to control hypercholesterolemia with appropriate diet, exercise, weight reduction in obese patients, and to treat other underlying medical problems (see INDICATIONS AND USAGE).

Lovastatin may elevate creatine phosphokinase and transaminase levels (see ADVERSE REACTIONS). This should be considered in the differential diagnosis of chest pain in a patient on therapy with lovastatin.

Eye: There was a high prevalence of baseline lenticular opacities in the patient population included in the clinical trials with lovastatin. During these trials the appearance of new opacities was noted. The causal relationship of lovastatin to these findings has not been established.

Of 431 patients examined with slit lamp at baseline and during therapy with lovastatin, 34 had opacities reported at the final examination (5 to 15 months after starting lovastatin) that were not noted at baseline. On the other hand, in 45 patients, opacities observed at baseline were not noted at the final examination, so that the prevalence did not increase. There was no clinically significant change in visual acuity in the patients who had new opacities reported, nor was any patient, including those with opacities noted at baseline, discontinued from therapy because of a decrease in visual acuity. Nevertheless, until further experience is obtained, it is recommended that patients placed on lovastatin therapy be examined with a slit lamp before or shortly after initiation of treatment and annually thereafter.

Homozygous Familial Hypercholesterolemia: MEVACOR® (Lovastatin, MSD) is less effective in patients with the rare homozygous familial hypercholesterolemia, possibly because these patients have no functional LDL receptors. MEVACOR appears to be more likely to raise serum transaminases (see ADVERSE REACTIONS) in these homozygous patients.

Drug Interactions: *Immunosuppressive Drugs, Gemfibrozil, Niacin (Nicotinic Acid), Erythromycin*. See WARNINGS, *Skeletal Muscle*.

Coumarin Anticoagulants: In a clinical trial in warfarin-treated patients designed specifically to observe a potential effect of lovastatin on the prothrombin time, lovastatin in dosages up to 40 mg b.i.d. did not produce any consistent alteration of the anticoagulant action of warfarin. However, since the drug was marketed, clinically evident bleeding and/or increased prothrombin time have been reported in a few patients taking coumarin anticoagulants concomitantly with lovastatin. The causal relationship to lovastatin is unclear. Nevertheless, it is recommended that in patients taking anticoagulants, prothrombin time be determined before starting lovastatin and frequently enough during early therapy to insure that no significant alteration of prothrombin time occurs. Once a stable prothrombin time has been documented, prothrombin times can be monitored at the intervals usually recommended for patients on coumarin anticoagulants. If the dose of lovastatin is changed, the same procedure should be repeated. Lovastatin therapy has not been associated with bleeding or with changes in prothrombin time in patients not taking anticoagulants.

Antipyrine: Antipyrine is a model for drugs metabolized by the microsomal hepatic enzyme system (cytochrome P450 system). Because lovastatin had no effect on the pharmacokinetics of antipyrine, interactions with other drugs metabolized via this mechanism are not expected.

Propranolol: In normal volunteers, there was no clinically significant pharmacokinetic or pharmacodynamic interaction with concomitant administration of single doses of lovastatin and propranolol.

Digoxin: In patients with hypercholesterolemia, concomitant administration of lovastatin and digoxin resulted in no effect on digoxin plasma concentrations.

Other Concomitant Therapy: Although specific interaction studies were not performed, in clinical studies, lovastatin was used concomitantly with beta blockers, calcium channel blockers, diuretics, and nonsteroidal anti-inflammatory drugs (NSAIDs) without evidence of clinically significant adverse interactions.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a 21-month carcinogenic study in mice, a statistically significant ($p < 0.05$) increase in the incidence of hepatocellular carcinomas and adenomas was observed at doses of 500 mg/kg/day (312 times the maximum recommended human dose) of lovastatin. These changes were not seen in mice given doses of 20 and 100 mg/kg/day (1.2 5 and 6.2 5 times the maximum recommended human dose).

A statistically significant increase ($p \leq 0.05$) in the incidence of pulmonary adenomas was seen in female mice receiving 500 mg/kg/day (312 times the maximum recommended human dose), no similar changes were seen in males at any dose or in females receiving 20 or 100 mg/kg/day (12.5 or 62.5 times the maximum recommended human dose). Because the incidence of pulmonary tumors was within the range of untreated animals in studies of similar duration, the relationship of this latter change to treatment is not known.

In addition, an increase in the incidence of papilloma in the non-glandular mucosa of the stomach was observed in mice receiving 100 and 500 mg/kg/day (6.2 5 and 31.2 times the maximum recommended human dose), no increase was seen at a dosage of 20 mg/kg/day (1.2 5 times the maximum recommended human dose). The glandular mucosa was not affected. The human stomach contains only glandular mucosa. Importantly, there is a strong association between this change and hyperplasia of the squamous epithelium (acanthosis) in this region, acanthosis is a characteristic change observed in the non-glandular mucosa of rodents treated with HMG-CoA reductase inhibitors and is most probably a result of inhibition of the reductase in this tissue.

Similar squamous epithelium is found in the esophagus and anorectal junction of the mouse and rat, however, no evidence of a similar drug-induced hyperplastic response was observed in these tissues in studies of up to 21 months in the mouse given up to 500 mg/kg/day (312 times the maximum recommended human dose), or in a study of 24 months in the rat given 180 mg/kg/day (112 times the maximum recommended human dose).

In a 24-month carcinogenicity study in rats, there was a positive dose response relationship for hepatocellular carcinogenicity in males (unadjusted $p = 0.025$). However, because the incidence of hepatocellular carcinogenicity observed in male rats in this study is similar to that observed spontaneously in this strain of rat, the implications of this finding are unclear.

Drug-related testicular atrophy, decreased spermatogenesis, spermatocytic degeneration and giant cell formation were seen in dogs starting at 20 mg/kg/day (1.2 5 times the maximum recommended human dose). The clinical significance of these findings is unclear.

No evidence of mutagenicity was observed in a microbial mutagen test using mutant strains of *Salmonella typhimurium* with or without rat or mouse liver metabolic activation. In addition, no evidence of damage to genetic material was noted in an *in vitro* alkaline elution assay using rat or mouse hepatocytes, a V-79 mammalian cell forward mutation study, an *in vitro* chromosome aberration study in CHO cells, or an *in vivo* chromosomal aberration assay in mouse bone marrow.

No drug-related effects on fertility were found in studies with rats.

Pregnancy: Pregnancy Category X. See CONTRAINDICATIONS.

Lovastatin has been shown to produce skeletal malformations in the rat fetus at doses of 800 mg/kg/day (500 times the maximum recommended human dose). At similar doses in mice, an increase in skeletal malformations was observed. These individual changes are within the range of those observed spontaneously in this strain of mouse. No drug-induced changes were seen in either species at doses of up to 80 mg/kg/day (50 times the maximum recommended human dose). No evidence of malformations was noted in rabbits at up to 15 mg/kg/day (highest tolerated dose – about 9 times the maximum recommended human dose). There are no data in pregnant women.

Nursing Mothers: Studies in rats have shown that lovastatin is excreted in the milk. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from MEVACOR, women taking lovastatin should not nurse their infants (see CONTRAINDICATIONS).

Pediatric Use: Safety and effectiveness in children have not been established. Because children are not likely to benefit from cholesterol lowering for at least a decade and because experience with this drug is limited (no studies in subjects below the age of 20 years), treatment of children w lovastatin is not recommended at this time.

ADVERSE REACTIONS: MEVACOR® (Lovastatin, MSD) is generally w tolerated; adverse reactions usually have been mild and transient. L than 1% of patients were discontinued from controlled clinical studies to adverse experiences attributable to MEVACOR. About 2% of patie were discontinued from all studies (controlled and uncontrolled) du adverse experiences attributable to MEVACOR, about one-third of th patients were discontinued due to increases in serum transaminases.

Clinical Adverse Experiences: Adverse experiences reported in patie treated with MEVACOR in controlled clinical studies are shown in the ta below.

	MEVACOR (N = 613) %	Placebo (N = 82) %	Cholestyramine (N = 88) %	Probu (N = %
Gastrointestinal				
Constipation	4.9	—	34.1	2
Diarrhea	5.5	4.9	8.0	10
Dyspepsia	3.9	—	13.6	3
Flatus	6.4	2.4	21.6	2
Abdominal pain/cramps	5.7	2.4	5.7	5
Heartburn	1.6	—	8.0	—
Nausea	4.7	3.7	9.1	6
Musculoskeletal				
Muscle cramps	1.1	—	1.1	—
Myalgia	2.4	1.2	—	—
Nervous System/Psychiatric				
Dizziness	2.0	1.2	—	1
Headache	9.3	4.9	4.5	8
Skin				
Rash/pruritus	5.2	—	4.5	—
Special Senses				
Blurred vision	1.5	—	1.1	3
Dysgeusia	0.8	—	1.1	—

Laboratory Tests: Marked persistent increases of serum transamina have been noted (see WARNINGS).

About 11% of patients had elevations of creatine phosphokinase (CI levels of at least twice the normal value on one or more occasions. corresponding values for the control agents were cholestyramine, 9%; probucol, 2%. This was attributable to the noncardiac fraction of CI Large increases in CPK have sometimes been reported (see WARNIN *Skeletal Muscle*).

Concomitant Therapy: In controlled clinical studies in which lovast was administered concomitantly with cholestyramine, no adverse re tions peculiar to this concomitant treatment were observed. The adve reactions that occurred were limited to those reported previously w lovastatin or cholestyramine. Other lipid-lowering agents were not adm istered concomitantly with lovastatin during controlled clinical studies uncontrolled clinical studies, most of the patients who have develo myopathy were receiving concomitant therapy with immunosuppres drugs, gemfibrozil, or niacin (nicotinic acid) (see WARNINGS, *Skel Muscle*).

Uncontrolled Clinical Studies: The adverse experiences observe uncontrolled studies were similar to those seen in controlled clin studies. Abnormal liver function tests were observed at a higher incide than in the controlled studies (see WARNINGS, *Liver Dysfunction*). My athy (myalgia with marked CPK elevations) was reported in appr imately 0.5% of patients (see WARNINGS, *Skeletal Muscle*).

Causal Relationship Unclear: *Nervous System*: Peripheral neurop has been reported; the relationship to lovastatin is uncertain. Vis evoked response, nerve conduction measurements, and electromyo phy in over 30 patients showed no evidence of neurotoxic effect lovastatin.

Special Senses: Of 431 patients examined with slit lamp at baseline during therapy with lovastatin, 34 had opacities reported at the final ex ination (5 to 15 months after starting lovastatin) that were not note baseline. On the other hand, in 45 patients, opacities observed at base were not noted at the final examination, so that the prevalence did increase (see PRECAUTIONS).

Post-marketing Experience: Additional adverse experiences occur since the drug was marketed are listed below.

Clinical Adverse Experiences

Gastrointestinal: Hepatitis, cholestatic jaundice, anore vomiting.

Hypersensitivity Reactions: An apparent hypersensitivity syndr has been reported rarely which has included one or more of the follow features: anaphylaxis, angioedema, lupus-like syndrome, polymya rheumatica, vasculitis, thrombocytopenia, leukopenia, hemolytic a mia, positive ANA, ESR increase, arthritis, arthralgia, urticaria, asthe photosensitivity, fever, chills, flushing, malaise, and dyspnea.

Nervous System/Psychiatric: Psychic disturbances, includ anxiety, paresthesia.

Skin: Erythema multiforme, including Stevens-Johnson s drome, toxic epidermal necrolysis.

Causal Relationship Unknown

Gastrointestinal: Pancreatitis, stomatitis.

Skin: Alopecia.

Nervous System/Psychiatric: Depression, insomnia.

Metabolic: Edema.

Clinical Laboratory Test Findings

Liver Function Tests: Liver function test abnormalities, includ elevated alkaline phosphatase and bilirubin.

Thyroid Function Tests: Rare reports of thyroid function test ab malities in patients taking concomitant thyroxine.

OVERDOSAGE: The oral LD_{50} of MEVACOR in mice is 20 g/kg.

Five healthy human volunteers have received up to 200 mg of lovast as a single dose without clinically significant adverse experiences. A cases of accidental overdosage have been reported, no patients had specific symptoms, and all patients recovered without sequelae. Th imum dose taken was 5 to 6 g.

Until further experience is obtained, no specific treatment of overd age with MEVACOR can be recommended.

The dialyzability of lovastatin and its metabolites in man is not know present.

DOSAGE AND ADMINISTRATION: The patient should be placed on a s dard cholesterol-lowering diet before receiving MEVACOR and sho continue on this diet during treatment with MEVACOR. MEVACOR sho be given with meals.

The recommended starting dose is 20 mg once a day given with evening meal. The recommended dosing range is 20 to 80 mg/day in gle or divided doses, the maximum recommended dose is 80 mg/ Adjustments of dosage should be made at intervals of 4 weeks or m Doses should be individualized according to the patient's response Tables I to IV under CLINICAL PHARMACOLOGY, *Clinical Studies* for response results).

For those patients with severely elevated serum cholesterol le (i.e., >300 mg/dL [7.8 mmol/L] on diet), MEVACOR may be initiated 4 mg/day.

In patients taking immunosuppressive drugs concomitantly lovastatin (see WARNINGS, *Skeletal Muscle*), the maximum rec mended dosage is 20 mg/day.

Cholesterol levels should be monitored periodically and consideration should be given to reducing the dosage of MEVACOR if cholesterol levels fall below the targeted range.

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For more detailed information, consult your MSD Representative or Prescribing Information, Merck Sharp & Dohme, Division of Mer Co., Inc., West Point, PA 19486. JDMC49R

ABSTRACTS SEPTEMBER 1991

(Oboler SK, Prochazka AV, Meyer TJ: Leg symptoms in outpatient veterans. West J Med 1991 Sep; 155:256-259)

In a survey of outpatients at the Denver Veterans Affairs Medical Center for common leg symptoms—515 questionnaires returned in a 3-week period—56% reported nocturnal leg cramps, 29% reported the restless leg syndrome, and 49% reported symptoms of peripheral neuropathy. Only 33% of patients had no symptoms relating to their legs. Patients often did not report these symptoms to their physician but were more likely to do so if the symptoms were frequent. Conditions especially related to leg symptoms were hypertension, peripheral vascular disease, coronary artery disease, cerebrovascular disease, kidney disease, and hypokalemia. Most patients did not receive effective therapy for these symptoms.

LEG CRAMPS
RESTLESS LEG SYNDROME
NOCTURNAL LEG CRAMPS
PERIPHERAL NEUROPATHY

(Oboler SK, Prochazka AV, Meyer TJ: Leg symptoms in outpatient veterans. West J Med 1991 Sep; 155:256-259)

In a survey of outpatients at the Denver Veterans Affairs Medical Center for common leg symptoms—515 questionnaires returned in a 3-week period—56% reported nocturnal leg cramps, 29% reported the restless leg syndrome, and 49% reported symptoms of peripheral neuropathy. Only 33% of patients had no symptoms relating to their legs. Patients often did not report these symptoms to their physician but were more likely to do so if the symptoms were frequent. Conditions especially related to leg symptoms were hypertension, peripheral vascular disease, coronary artery disease, cerebrovascular disease, kidney disease, and hypokalemia. Most patients did not receive effective therapy for these symptoms.

LEG CRAMPS
RESTLESS LEG SYNDROME
NOCTURNAL LEG CRAMPS
PERIPHERAL NEUROPATHY

(Oboler SK, Prochazka AV, Meyer TJ: Leg symptoms in outpatient veterans. West J Med 1991 Sep; 155:256-259)

In a survey of outpatients at the Denver Veterans Affairs Medical Center for common leg symptoms—515 questionnaires returned in a 3-week period—56% reported nocturnal leg cramps, 29% reported the restless leg syndrome, and 49% reported symptoms of peripheral neuropathy. Only 33% of patients had no symptoms relating to their legs. Patients often did not report these symptoms to their physician but were more likely to do so if the symptoms were frequent. Conditions especially related to leg symptoms were hypertension, peripheral vascular disease, coronary artery disease, cerebrovascular disease, kidney disease, and hypokalemia. Most patients did not receive effective therapy for these symptoms.

LEG CRAMPS
RESTLESS LEG SYNDROME
NOCTURNAL LEG CRAMPS
PERIPHERAL NEUROPATHY

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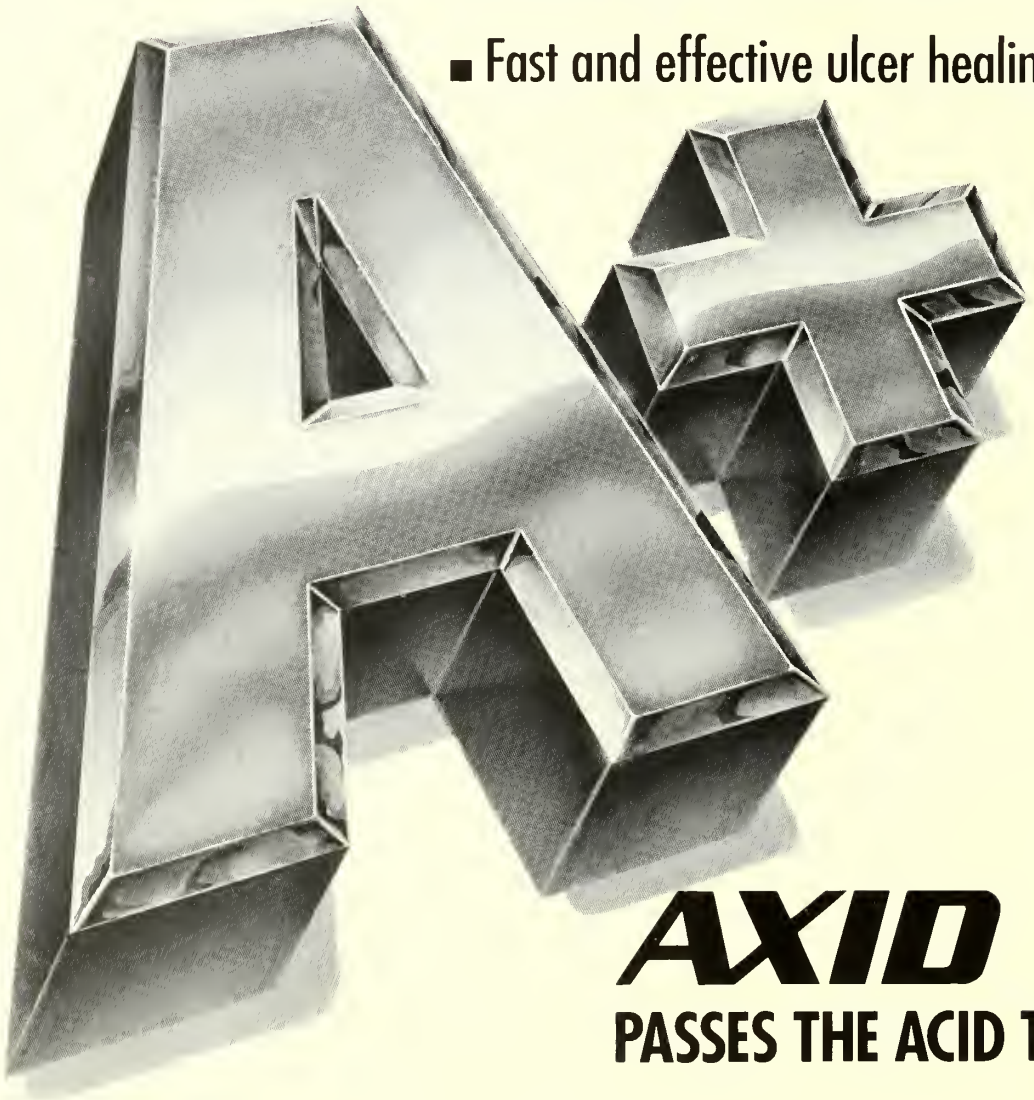

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See adjacent page for references and brief summary of prescribing information.

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Indications and Usage: 1. *Active duodenal ulcer* – for up to 8 weeks of treatment. Most patients heal within 4 weeks.

2. *Maintenance therapy* – for healed duodenal ulcer patients at a reduced dosage of 150 mg h.s. The consequences of therapy with Axid for longer than 1 year are not known.

Contraindications: Known hypersensitivity to the drug. Because cross sensitivity in this class of compounds has been observed, H_2-receptor antagonists, including Axid, should not be administered to patients with a history of hypersensitivity to other H_2-receptor antagonists.

Precautions: *General* – 1. Symptomatic response to nizatidine therapy does not preclude the presence of gastric malignancy.

2. Dosage should be reduced in patients with moderate to severe renal insufficiency.

3. In patients with normal renal function and uncomplicated hepatic dysfunction, the disposition of nizatidine is similar to that in normal subjects.

Laboratory Tests – False-positive tests for urobilinogen with Multistix® may occur during therapy.

Drug Interactions – No interactions have been observed with theophylline, chlordiazepoxide, lorazepam, lidocaine, phenytoin, and warfarin. Axid does not inhibit the cytochrome P-450 enzyme system, therefore, drug interactions mediated by inhibition of hepatic metabolism are not expected to occur. In patients given very high doses (3,900 mg) of aspirin daily, increased serum salicylate levels were seen when nizatidine, 150 mg b.i.d., was administered concurrently.

Carcinogenesis, Mutagenesis, Impairment of Fertility – A 2-year oral carcinogenicity study in rats with doses as high as 500 mg/kg/day (about 80 times the recommended daily therapeutic dose) showed no evidence of a carcinogenic effect. There was a dose-related increase in the density of enterochromaffin-like (ECL) cells in the gastric oxyntic mucosa. In a 2-year study in mice, there was no evidence of a carcinogenic effect in male mice, although hyperplastic nodules of the liver were increased in the high-dose males as compared with placebo. Female mice given the high dose of Axid (2,000 mg/kg/day, about 330 times the human dose) showed marginally statistically significant increases in hepatic carcinoma and hepatic nodular hyperplasia with no numerical increase seen in any of the other dose groups. The rate of hepatic carcinoma in the high-dose animals was within the historical control limits seen for the strain of mice used. The female mice were given a dose larger than the maximum tolerated dose, as indicated by excessive (30%) weight decrement as compared with concurrent controls and evidence of mild liver injury (transaminase elevations). The occurrence of a marginal finding at high dose only in animals given an excessive and somewhat hepatotoxic dose, with no evidence of a carcinogenic effect in rats, male mice, and female mice (given up to 360 mg/kg/day, about 60 times the human dose), and a negative mutagenicity battery are not considered evidence of a carcinogenic potential for Axid.

Axid was not mutagenic in a battery of tests performed to evaluate its potential genetic toxicity, including bacterial mutation tests, unscheduled DNA synthesis, sister chromatid exchange, mouse lymphoma assay, chromosome aberration tests, and a micronucleus test.

In a 2-generation, perinatal and postnatal fertility study in rats, doses of nizatidine up to 650 mg/kg/day produced no adverse effects on the reproductive performance of parental animals or their progeny.

Pregnancy – Teratogenic Effects – Pregnancy Category C – Oral reproduction studies in rats at doses up to 300 times the human dose and in Dutch Belted rabbits at doses up to 55 times the human dose revealed no evidence of impaired fertility or teratogenic effect; but, at a dose equivalent to 300 times the human dose, treated rabbits had abortions, decreased number of live fetuses, and depressed fetal weights. On intravenous administration to pregnant New Zealand White rabbits, nizatidine at 20 mg/kg produced cardiac enlargement, coarctation of the aortic arch, and cutaneous edema in 1 fetus, and at 50 mg/kg, it produced ventricular anomaly, distended abdomen, spina bifida, hydrocephaly, and enlarged heart in 1 fetus. There are, however, no adequate and well-controlled studies in pregnant women. It is also not known whether nizatidine can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Nizatidine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers – Studies in lactating women have shown that 0.1% of an oral dose is secreted in human milk in proportion to plasma concentrations. Because of growth depression in pups reared by treated lactating rats, a decision should be made whether to discontinue nursing or the drug, taking into account the importance of the drug to the mother.

Pediatric Use – Safety and effectiveness in children have not been established.

Use in Elderly Patients – Healing rates in elderly patients were similar to those in younger age groups as were the rates of adverse events and laboratory test abnormalities. Age alone may not be an important factor in the disposition of nizatidine. Elderly patients may have reduced renal function.

Adverse Reactions: Clinical trials of varying durations included almost 5,000 patients. Among the more common adverse events in domestic placebo-controlled trials of over 1,900 nizatidine patients and over 1,300 on placebo, sweating (1% vs 0.2%), urticaria (0.5% vs <0.01%), and somnolence (2.4% vs 1.3%) were significantly more common with nizatidine. It was not possible to determine whether a variety of less common events were due to the drug.

Hepatic – Hepatocellular injury (elevated liver enzyme tests or alkaline phosphatase) possibly or probably related to nizatidine occurred in some patients. In some cases, there was marked elevation (>500 IU/L) in SGOT or SGPT and, in a single instance, SGPT was >2,000 IU/L. The incidence of elevated liver enzymes overall and elevations of up to 3 times the upper limit of normal, however, did not significantly differ from that in placebo patients. All abnormalities were reversible after discontinuation of Axid. Since market introduction, hepatitis and jaundice have been reported. Rare cases of cholestatic or mixed hepatocellular and cholestatic injury with jaundice have been reported with reversal of the abnormalities after discontinuation of Axid.

Cardiovascular – In clinical pharmacology studies, short episodes of asymptomatic ventricular tachycardia occurred in 2 individuals administered Axid and in 3 untreated subjects.

CNS – Rare cases of reversible mental confusion have been reported.

Endocrine – Clinical pharmacology studies and controlled clinical trials showed no evidence of antiandrogenic activity due to nizatidine. Impotence and decreased libido were reported with equal frequency by patients on nizatidine and those on placebo. Gynecomastia has been reported rarely.

Hematologic – Fatal thrombocytopenia was reported in a patient treated with nizatidine and another H_2-receptor antagonist. This patient had previously experienced thrombocytopenia while taking other drugs. Rare cases of thrombocytopenic purpura have been reported.

Integumental – Sweating and urticaria were reported significantly more frequently in nizatidine- than in placebo-treated patients. Rash and exfoliative dermatitis were also reported.

Hypersensitivity – As with other H_2-receptor antagonists, rare cases of anaphylaxis following nizatidine administration have been reported. Rare episodes of hypersensitivity reactions (eg, bronchospasm, laryngeal edema, rash, and eosinophilia) have been reported.

Other – Hyperuricemia unassociated with gout or nephrolithiasis was reported. Eosinophilia, fever, and nausea related to nizatidine have been reported.

Overdosage: Overdoses of Axid have been reported rarely. If overdosage occurs, activated charcoal, emesis, or lavage should be considered along with clinical monitoring and supportive therapy. Renal dialysis does not substantially increase clearance of nizatidine due to its large volume of distribution.

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References
1. Data on file, Lilly Research Laboratories
2. *Scand J Gastroenterol* 1987,22(suppl 136):61-70.
3. *Scand J Gastroenterol* 1987,22(suppl 136) 47-55.
4. *Am J Gastroenterol* 1989,84 769-774

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Additional information available to the profession on request

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FREE HIV RISK ASSESSMENT PROGRAM AVAILABLE

CMA's Department of Physician Education has produced a new CME program, "HIV Risk Assessment: Methods and Guidelines," which is available free to physicians. This program teaches effective strategies developed by expert physicians to identify patients who are potentially at risk for HIV infection. Worth one hour of CME Category I credit, the program is designed for groups of 5-20 physicians.

The program features CMA's award-winning, 11-minute video, "Let's Talk," which highlights several methods physicians can use to perform HIV assessment with patients. Participants receive a course outline, camera-ready slide reproductions, a compilation of state laws pertaining to HIV/AIDS, community resource guide to HIV testing and counseling, risk assessment guidelines, and a model HIV consent form and patient information pamphlet.

Those interested in taking part in this unique CME program should contact Amy Wright in CMA's Department of Physician Education at 415/882-5186.

LET'S TALK
ABOUT AIDS RISK

CONTINUING MEDICAL EDUCATION

(Continued from Page 220)

November 2—**Cardiac Risk Reduction Conference.** UCD at Radisson Hotel, Sacramento. Sat. Contact: UCD.

November 8-9—**Coronary Interventions: 1991.** Scripps Clinic and Research Foundation at La Jolla Marriott Hotel. Fri-Sat. 14 hrs. $550. Contact: Susan Buntjer, 400S, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

CRITICAL CARE

October 17-19—**Traumatic Brain Injury.** UCD at Radisson Hotel, Sacramento. Thurs-Sat. 23 hrs. $435. Contact: UCD.

October 17-19—**10th Annual Recent Advances in Pulmonary and Critical Care Medicine.** UCSF at Sheraton Palace Hotel, San Francisco. Thurs-Sat. 15 hrs. $395. Contact: UCSF.

October 19—**Norman Sharrer Symposium: Critical Care Revisited.** Kaweah Delta District Hospital at Radisson Hotel, Visalia. Sat. 6 hrs. $30. Contact: Brooke Mack, (209) 625-7308.

DERMATOLOGY

November 2—**Dermatology Update: 1991.** Sutter Health at Sacramento Association of Realtors. Sat. Contact: Sutter Health Medical Education, 2800 L St, Sacramento 95816. (800) 777-0231.

November 8-10—**Pediatric Dermatology and Wound Management: Above and Below the Surface.** Children's Hospital Oakland at Monterey Conference Center, Monterey. Fri-Sun. 12 hrs. $300. Contact: Children's Hospital, 747-52nd St, Oakland 94609. (415) 428-3021.

January 17-19—**Practical Dermatology and Dermatologic Office Procedures for the Primary Care Physician.** UCSD at Hyatt Regency, La Jolla. Fri-Sun. 20 hrs. Contact: Jacqueline Shiller, Box 84296, San Diego 92138. (619) 223-2997.

January 31-February 2—**Cutaneous Malignancies: 1992 Skin Cancer Update.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Fri-Sun. 18 hrs. Contact: Susan Buntjer, Scripps Clinic and Research Foundation, 10666 N Torrey Pines Road, La Jolla 92037. (619) 554-8556.

KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690 (415) 541-0900.

DREW: Charles R Drew Postgraduate Medical School
Contact: Herbert M Thomas, MD, MPH, Director of CME, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th St, Los Angeles 90059. (213) 603-3183.

LLU: Loma Linda University
Contact. James J. Couperus, MD, Associate Dean for Educational Affairs, Loma Linda University School of Medicine, Loma Linda 92350

PMC: Pacific Medical Center
Contact. Continuing Education, Pacific Medical Center, PO Box 7999, San Francisco 94120. (415) 563-4321, ext 2761.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Medical School Office Building, Suite X-365, Stanford 94305-6114 (415) 723-5594

UCD: University of California, Davis
Contact. Ruth Feryok, Director, Office of Continuing Medical Education, University of California, Davis, School of Medicine, 2701 Stockton Blvd, Sacramento 95817. (916) 734-5390.

UCI: University of California, Irvine
Contact. Melvin I. Marks, MD, Director, Memorial/UCI Center for Health Education, Long Beach Memorial Medical Center, 2801 Atlantic Ave, PO Box 1428, Long Beach, California 90801-1428. (213) 595-3811

UCLA: University of California, Los Angeles Extension
Contact Martin D Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, PO Box 24902, UCLA, Los Angeles 90024. (213) 825-8423.

UCSD: University of California, San Diego
Contact Office of Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (619) 534-3940.

UCSF: University of California, San Francisco
Contact. Janet Johnson, Administrative Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 476-4251.

USC: University of Southern California
Contact Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 1975 Zonal Ave, KAM314, Los Angeles 90033 (213) 224 7051.

February 27—**Problems of the Aging Skin.** Stanford Medical Center at Palm Springs. Thurs-Sun. Contact: Pamela Bain, R-144, Stanford 94305. (415) 723-7854.

EMERGENCY MEDICINE

October 9-13—**13th Biannual Wound Management Workshop.** UCSD at San Diego Hilton Beach & Tennis Resort. Wed-Sun. Contact: UCSD.

October 21-25—**Emergency Medicine Symposia I.** UCSD at La Jolla Marriott. Mon-Fri. Contact: UCSD.

October 28-November 1—**Twentieth Annual Topics in Emergency Medicine.** UCSF at Sheraton Palace Hotel, San Francisco. Mon-Fri. 32 hrs. $510. Contact: UCSF.

November 11-15—**Emergency Medicine Symposia III.** UCSD at San Diego Hilton Beach & Tennis Resort. Mon-Fri. Contact: UCSD.

November 16-17—**Biomechanics of Trauma.** UCSD at San Diego Marriott. Sat-Sun. Contact: UCSD.

December 9-13—**Emergency Medicine Symposia II.** UCSD at Basic Science Building, La Jolla. Mon-Fri. Contact: UCSD.

February 23-28—**Emergency Medicine.** UCD at Incline Village, Nevada. Sun-Fri. Contact: UCD.

ENDOCRINOLOGY AND METABOLISM

October 18-20—**Obesity Update: Assessment & Treatment.** UCD at Hyatt Regency, Sacramento. Fri-Sun. Contact: UCD.

October 20-23—**Joint Annual Research Conference on Obesity & Food Intake.** North American Association of the Study of Obesity & Society for Study of Ingestive Behavior at Hyatt Regency, Saramento. Sun-Wed. Contact: UCD.

November 1-2—**Practical Methods in Diabetes.** Memorial/UCI Center for Health Education at Meridien Newport Beach. Fri-Sat. Contact: UCD.

FAMILY PRACTICE/PRIMARY CARE

September 28—**Primary Care Issues in Atherosclerosis.** Alta-Bates Herrick Hospital at Hospital Auditorium. Sat. 7 hrs. $65. Contact: Mary Grim, (415) 540-1420.

October 2-4—**Sixth Annual Primary Care Medicine: Principles and Practice.** UCSF at Sheraton Palace Hotel, San Francisco. Wed-Fri. 19 hrs. $465. Contact: UCSF.

October 18-20—**Office Orthopedics for the Primary Care Physician.** Sharp Memorial Hospital at San Diego Princess at Vacation Village. Fri-Sun. 20 hrs. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

November 15-17—**Family Practice Today & Tomorrow.** UCSD at Sheraton Hotel, San Diego. Fri-Sun. Contact: UCSD.

February 14-16—**Office Gynecology for the Primary Care Physician.** SDSU at Hyatt Islandia, San Diego. Fri-Sun. 20 hrs. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

February 13-15—**Current Concepts in Cancer Management: A Symposium for Primary Care Physicians and Cancer Care Providers.** Hoag Memorial Center at Newport Beach Marriott. Thurs-Sat. $350. Contact: Meeting Management, 5665 Oberlin, Ste 110, San Diego 92121. (619) 453-6222.

February 17-19—**Issues in Men's Health.** SDSU at Hyatt Islandia, San Diego. Mon-Wed. 20 hrs. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

GASTROENTEROLOGY

September 20-22—**Gastroenterology: Recent Developments in Theory & Practice.** UCSF at Sheraton Palace Hotel, San Francisco. Fri-Sun. 18 hrs. $420. Contact: UCSF.

February 29-March 1—**Endoscopy Update 1992.** Southern California Society for Gastroenterology at Century Plaza Hotel, Los Angeles. Sat-Sun. Contact: Joyce Fried, University of California Brain Research Institute, Los Angeles 90024.

INFECTIOUS DISEASES

September 21—**AIDS Update.** Sutter Health at Sacramento Inn. Sat. Contact: Sutter Health, 2800 L St, Sacramento 95816. (800) 777-0231.

February 7-8—**10th Annual Infectious Disease.** UCD. Fri-Sat. Contact: UCD.

(Continued on Page 238)

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(Continued from Page 236)

INTERNAL MEDICINE

November 1-3—**Diagnosis & Management of Chronic Major Vessel Thromboembolic Pulmonary Hypertension.** UCSD at Sheraton Harbor Island Hotel, San Diego. Sun-Tues. Contact: UCSD.

November 7-9—**San Francisco Otology Update: 1991.** UCSF. Thurs-Sat. 22 hrs. Contact: UCSF.

December 5—**Common Musculoskeletal Problems—Knee.** VA Medical Center Sepulveda. Thurs. 5.5 hrs. Contact: Arun Mehta, MD, VA Med Ctr, (818) 895-9344.

December 6-7—**Clinical Applications of New Advances in Internal Medicine.** UCD at Cancer Center Auditorium. Fri-Sat. Contact: UCD.

February 6-8—**Allergy Diagnosis.** UCSD at La Jolla Village Inn. Thurs-Sat. 20 hrs. $290. Contact: Janice Turner, PO Box 2586, La Jolla 92038. (619) 459-1564.

NEUROLOGY

October 17-19—**Child Neurology in the Decade of the Brain.** UCSF at Hyatt Regency Hotel, San Francisco. Thurs-Sat. 18.5 hrs. $345. Contact: UCSF.

November 1-2—**Transcranial Doppler and Cerebral Blood Flow Monitoring.** UCLA at Sheraton Miramar Hotel, Santa Monica. Fri-Sat. 12.5 hrs. Contact: UCLA.

January 1-February 1—**15th Annual: Neurology for Non-Neurologists.** UCSD at Omni San Diego Hotel. Thurs-Sat. 21 hrs. $425. Contact: UCSD.

February 13-15—**25th Annual Recent Advances in Neurology.** UCSF at San Francisco. Thurs-Sat. 15 hrs. Contact: UCSF.

OB/GYN

September 26-29—**Advanced Fetal Heart Rate Monitoring.** Memorial/UCI Center for Health Education. Thurs-Sun. Contact: UCI.

October 4-6—**3rd Annual Advanced Obstetrical & Transvaginal Ultrasound.** Memorial/UCI Center for Health Education at Doubletree Hotel/UCI Medical Center, Orange. Fri-Sun. Contact: UCI.

October 23-26—**Trends in OB-GYN Management.** Sharp Memorial Hospital at Hotel del Coronado, San Diego. Wed-Sat. 16 hrs. Contact: Debra L. Gist, 7901 Frost St, San Diego 92123-2788. (619) 541-4530.

November 8-10—**Current Issues in Perinatal Medicine.** Memorial/UCI at Marriott's Rancho Las Palmas Resort, Palm Springs. Fri-Sun. Contact: UCI.

November 18-23—**14th Annual Review Course in Clinical OB/GYN and Gynecological Histopathology.** Memorial/UCI Center for Health Education at Westin South Coast Plaza, Costa Mesa. Mon-Sat. Contact: UCI.

January 16-19—**OB/GYN and Ultrasound.** UCSD at Hotel del Coronado, San Diego. Thurs-Sun. 20 hrs. $450. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

February 2-6—**Ambulatory Gynecology.** UCD at Hyatt Lake Tahoe, Incline Village, Nevada. Sun-Thurs. Contact: UCD.

February 13-16—**47th Annual Postgraduate Assembly.** OB/GYN Assembly of Southern California at Beverly Hilton, Beverly Hills. Thurs-Sun. 28 hrs. Contact: OB/GYN Assembly, 5820 Wilshire Blvd, #500, Los Angeles 90036. (213) 937-5514.

OCCUPATIONAL/ENVIRONMENTAL

September 28—**Indoor Air and Radon: Reducing Health Risks Forum.** CMA, AMA, and US EPA at LAX Marriott, Los Angeles. Sat. 4 hrs. Contact: Vickie Grosso. (312) 464-4574.

October 10-13—**35th Annual Western Occupational Health Conference: Changing Themes in Occupational Medicine.** Western Occupational Medical Association at Doubletree Hotel, Monterey. Thurs-Sun. Contact: Kate Larsen, (415) 764-4803.

October 21-25—**Sports Medicine Update.** Memorial/UCI Center for Health Education in Hawaii. Mon-Fri. Contact: UCI.

October 21-November 1—**Occupational and Environmental Medicine: Session II.** UCSF at Miyako Hotel, San Francisco. Mon-Fri. 80 hrs. $1200. Contact: UCSF.

October 28-November 1—**Advances in Occupational and Environmental Medicine.** UCSF at Miyako Hotel, San Francisco. Mon-Fri. 40 hrs. $600. Contact: UCSF.

January 27-February 7—**Occupational and Environmental Medicine Series: Session I.** UCSF at Miyako Hotel, San Francisco. Mon-Fri. 80 hrs. $1200. Contact: UCSF.

February 10-14—**Occupational and Environmental Medicine: Session III.** UCSF at Miyako Hotel Japan Center, San Francisco. Mon-Fri. 40 hrs. $600. Contact: UCSF.

February 12-16—**Team Physician Course.** American College of Sports Medicine at Wyndham Hotel, Palm Springs. Wed-Sun. Contact: ACMS, PO Box 1440, Indianapolis, IN 46202-1440. (317) 637-9200.

ONCOLOGY

October 5—**G.I. Cancer Symposium.** Sutter Health at Hyatt Regency, Sacramento. Sat. Contact: Sutter Health, 2800 L St, Sacramento 95816. (800) 777-0231.

October 14-20—**17th Annual Lymphoma Course.** Scripps Clinic and Research Foundation, La Jolla. Mon-Fri. 25 hrs. $550. Contact: Laurel Steigerwald, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

October 19—**10th Annual Cancer Symposium: Update & Overview.** Hi Desert Joint Cancer Program at Bally's Hotel, Las Vegas. Sat. $75. Contact: Alice Williams, 18300 Hwy 18, Apple Valley 92307. (619) 242-2311, ext 445.

November 21-23—**3rd Annual Symposium on Diagnosis and Treatment of Musculoskeletal Tumors.** UCD at Hyatt Regency, Sacramento. Thurs-Sat. 16 hrs. $450. Contact: UCD.

February 17-19—**Clinical Hematology and Oncology: 1992.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Mon-Wed. 18 hrs. $385. Contact: Susan Buntjer, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

OPHTHALMOLOGY

September 13-15—**Uveitis and Retina Frontiers—Diagnostic, Medical and Surgical Approaches.** UCSF at Carmel Valley Ranch Resort. Fri-Sun. Contact: UCSF.

October 13-17—**Joint Meeting of the American Academy of Ophthalmology and Pan-American Association of Ophthalmology** at Anaheim Convention Center. Sun-Thurs. Contact: AAO, PO Box 7424, San Francisco 94120. (415) 561-8500.

January 31-February 4—**11th Annual Squaw Valley Retina Symposium.** Alta-California Ophthalmological Society at Resort at Squaw Creek, Olympic Valley. Fri-Tues. 16 hrs. Contact: Richard Murray, 2701 Eye St, Sacramento 95816. (916) 442-4975.

ORTHOPEDICS

September 28—**Orthopedics From Head to Toe.** Sutter Health at Hilton Inn, Sacramento. Sat. Contact: Sutter Health, 2800 L St, Sacramento 95816. (800) 777-0231.

October 17-18—**4th Annual International Symposium on Custom Prostheses.** Sutter Health at Stanford Court Nob Hill, San Francisco. 20 hrs. $450. Contact: Sutter Health, 2800 L St, Sacramento 95816. (800) 777-0231.

PAIN MANAGEMENT

September 28—**Pain: Diagnosis, Treatment and Management.** Scripps Clinic and Research Foundation, La Jolla. Sat. 19 hrs. $75. Contact: Laurel Steigerwald, 10666 N Torrey Pines Blvd, La Jolla 92037. (619) 554-8556.

October 26—**Current Concepts in Pain: Diagnosis and Management.** Antelope Valley Hospital Medical Center at Antelope Valley Inn and Convention Center, Lancaster. Sat. 5 hrs. $60. Contact: Pamela Stones, (805) 949-5942.

November 15-16—**Pain Management.** UCD at Sterling Hotel, Napa. Fri-Sat. Contact: UCD.

December 11-15—**American Back Society Fall Symposium on Back Pain.** St. Francis Memorial Hospital Spine Center at Marriott, San Francisco. Wed-Sun. Contact: Aubrey Swartz, 2647 E 14th St, #401, Oakland 94601. (415) 536-9929.

February 19-22—**The Practicing Physician's Approach to the Difficult Headache Patient.** University of Chicago School of Medicine at Wyndham Hotel, Palm Springs. Wed-Sat. 15 hrs. Contact: Idell Applebaum, Diamond Headache Clinic, 5252 N Western Ave, Chicago, IL 60625. (312) 878-0396.

(Continued on Page 240)

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(Continued from Page 238)

PATHOLOGY

October 12—**Thirty-first Annual Scientific Symposium on Kidney Disease.** National Kidney Foundation of Southern California at La Jolla Marriott, La Jolla. Sat. Contact: Sylvie Tarro, (213) 641-8152.

PEDIATRICS

September 23-27—**Pediatrics in Paradise.** Valley Children's Hospital at Hyatt Regency, Kauai, Hawaii. Mon-Fri. 20 hrs. Contact: Valley Children's Hospital, Marketing and Planning, 3151 N Millbrook, Fresno 93703.

October 16-19—**16th Annual Pediatrics for the Practitioner.** Memorial/UCI Center for Health Education at Mauna Kea Beach Hotel, Kamuela, Hawaii. Wed-Sat. Contact: UCI.

November 20-23—**Pediatric Infectious Disease Seminar.** University of Toronto at Four Seasons Hotel, Newport Beach. Wed-Sat. Contact: University of Toronto, Medical Science Bldg, Toronto, Ontario M5S 1A8. (416) 978-2718.

January 22-25—**San Diego Conference on Responding to Child Maltreatment.** Children's Hospital at Hyatt Regency Hotel, La Jolla. Wed-Sat. Contact: Children's Hospital, 8001 Frost St, San Diego 92123. (619) 495-4940.

February 7-9—**Current Concepts in Pediatric Medicine: 1992.** Children's Hospital San Diego at Hyatt Islandia Hotel, San Diego. Fri-Sun. 18 hrs. Children's Hospital, (619) 576-4072.

PSYCHIATRY

October 5—**The Healing Response in Mind-Body Therapy.** UCLA at Dodd Hall. Sat. 6 hrs. $105. Contact: UCLA.

November 8-10—**37th Annual Group Therapy Symposium.** UCSF at Handlery Union Square Hotel, San Francisco. Fri-Sun. Contact: UCSF.

RADIOLOGY

September 14-15—**Sonography Registry Review.** UCSD at Hotel del Coronado, San Diego. Sat-Sun. 16 hrs. $200. Contact: Dawne Ryals, Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

September 23-26—**Applied Ultrasound: Accent on Doppler.** University of Alabama at Birmingham at Ritz-Carlton Resort Hotel, Laguna Niguel. Mon-Thurs. Contact: Dawne Ryals, Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

September 25-28—**Diagnosis of Musculoskeletal Disorders: State of the Art.** International Skeletal Society at Hotel del Coronado, San Diego. Wed-Sat. 28 hrs. $450. Contact: Dawne Ryals, Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

October 3-6—**Current Concepts of Magnetic Resonance Imaging.** Stanford University Medical Center at Silverado Country Club and Resort, Napa Valley. Thurs-Sun. 19 hrs. $530. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

October 12-13—**Ultrasound: 1991.** UCD at Red Lion Inn, Sacramento. Sat-Sun. 10 hrs. $215. Contact: UCD.

October 17-20—**1991 Annual Scientific Meeting.** Western Neuroradiological Society at Ritz Carlton Resort, Laguna Niguel. Thurs-Sun. Contact: Dawne Ryals, Ryals & Associates, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

October 20—**Magnetic Resonance Angiography.** UCSF at Hyatt Regency Hotel, San Francisco. Sun. 7 hrs. Contact: UCSF.

October 21-25—**Clinical Magnetic Resonance Imaging.** UCSF at Hyatt Regency Hotel, San Francisco. Mon-Fri. 32 hrs. $595. Contact: UCSF.

October 26-27—**Advanced Imaging of the Musculoskeletal System.** UCSD at Hotel del Coronado, San Diego. Sat-Sun. 9 hrs. $225. Contact: Dawne Ryals, Ryals & Associates, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

October 26-27—**Vascular Ultrasound: State of the Art.** UCSF at Ritz-Carlton Hotel, San Francisco. Sat-Sun. 12 hrs. $285. Contact: UCSF.

October 28-November 1—**Sixteenth Annual Postgraduate Radiology Course.** UCSD at Hotel del Coronado, San Diego. Mon-Fri. 28.25 hrs. $550. Contact: Dawne Ryals, Ryals & Associates, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

November 1-3—**11th Annual Interventional Radiology Course.** UCSD at Hotel del Coronado, San Diego. Fri-Sun. 15 hrs. $375. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

November 4-8—**Diagnostic Radiology Seminars.** UCSF at Hyatt Regency, Maui, Hawaii. Mon-Fri. 24 hrs. $595. Contact: UCSF.

November 15-17—**Advanced Seminars in Diagnostic Imaging.** UCSD at Ritz-Carlton Hotel, Laguna Niguel. Fri-Sun. $400. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

January 10-12—**Advanced Seminars in Diagnostic Imaging.** UCSD at Ritz-Carlton Resort Hotel, Laguna Niguel. Fri-Sun. 15 hrs. $400. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925 (404) 641-9773.

January 12-16—**Diagnostic Imaging Update: Body Imaging, Mammography, Neuroradiology and Pediatrics.** Stanford University Medical Center at Ritz-Carlton Palm Beach. Sun-Thurs. 23.5 hrs. $550. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

February 4-7—**Advanced Seminars in Diagnostic Imaging.** UCSD at Le Meridien Hotel, Coronado. Tues-Fri. 20 hrs. $500. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

February 10-13—**Mammographically Detected Early Breast Cancer.** University of Alabama at Birmingham at Ritz-Carlton, Rancho Mirage. Mon-Thurs. 18 hrs. $450. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

February 24-28—**Diagnostic Imaging Update: Body Imaging, Mammography, MRI and Interventional.** Stanford University Medical Center at Ritz-Carlton Mauna Lani, Hawaii. Mon-Fri. 23.5 hrs. $550. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

February 27-March 1—**Advanced Seminars in Diagnostic Imaging.** UCSD at Ritz-Carlton, Laguna Niguel. Thurs-Sun. 20 hrs. $500. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

REHABILITATIVE/THERAPEUTIC

October 5—**Antithrombotic Therapy.** UCD at Cancer Center Auditorium. Sat. 6 hrs. Contact: UCD.

November 14-16—**3rd Triennial Symposium on New Directions in Antiviral Chemotherapy.** UCSF at Sheraton Palace Hotel, San Francisco. Thurs-Sat. 19 hrs. $200. Contact: UCSF.

SURGERY

October 10-13—**Wound Management Workshop: October.** UCSD at San Diego Hilton Beach and Tennis Resort. Thurs-Sun. 18 hrs. $435. Contact: Edith Bookstein, PO Box 2586, La Jolla 92038. (619) 454-3212.

October 27-30—**Preparing for Surgery: Medical Evaluation of the Preoperative Patient.** American College of Physicians and UCD at La Playa Hotel, Carmel. Sun-Wed. Contact: ACP, Independence Mall West, 6th St at Race, Philadelphia, PA 19106-1572. (800) 523-1546, ext. 2429.

November 2-9—**13th International Seminar on Operative Arthroscopy.** UCLA at Ritz-Carlton, Mauna Lani Resort, Hawaii. 1 week. 37 hrs. $995. Contact: UCLA.

February 8-11—**International Symposium on Hair Replacement Surgery.** American Academy of Facial Plastic and Reconstructive Surgery at Century City J W Marriott, Los Angeles. Sat-Tues. Contact: Sharon Clawson, (213) 278-8823.

GENERAL/MULTIDISCIPLINARY

September 28—**7th Annual Physicians' Conference on Drugs and Alcohol.** UCLA at Factor Auditorium. Mon. 6 hrs. Contact: UCLA.

October 24-26—**Medicine Today.** UCSD at Price Center. Sat-Sun. Contact: UCSD.

November 10—**Management of Cranial Base Disease.** UCSF Multidisciplinary Panel on Skull Base Diseases at Ritz Carlton Hotel, San Francisco. Sun. 8 hrs. $100. Contact: UCSF.

December 9-10—**Clinical Care of the AIDS Patient.** UCSF at San Francisco Marriott Hotel. Mon-Tues. 13 hrs. $250. Contact: UCSF.

COLORADO

This listing of continuing medical education programs in Colorado is compiled by the Denver Medical Society. To list CME programs here, please send information at least two months in advance to: Mr Robert L. Kennedy, Denver Medical Society, 1850 Williams Street, Denver, CO 80218; or telephone (303) 377-1850.

Brochures, course information, and registration forms are available from the contact person or organization.

(Continued on Page 244)

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Our readership represents all specialties of medicine. We wish to receive and publish manuscripts that are valid, important, lively, well-written, and succinct. They should be of interest to a broad range of busy practitioners, students, researchers, and scholars who have a clinical orientation. The purpose of a paper or letter may be to alert, review, discuss—above all, to teach. Titles should be short and intriguing. Avoid jargon, the overuse of abbreviations and acronyms, sexist language, redundancies, or expendable words and phrases (see *AMA Manual of Style*, 8th Edition).

Manuscript Information

Manuscripts should be sent to the Editor, Linda Hawes Clever, MD, *The Western Journal of Medicine*, 221 Main Street, San Francisco, California 94105. Manuscripts must be original, not previously published, and not under consideration by another publication. If preliminary data were included in another presentation or publication, that should be noted in the cover letter and a copy of that publication should be included.

Manuscripts should not exceed 3,000 words (15 double-spaced pages). Case Reports, Alerts, and Notices should not exceed 1,500 words. Lessons From the Practice should not exceed 1,000 words.

Manuscripts, except for Case Reports, Epitomes, and Lessons From the Practice, should include an abstract of no more than 200 words summarizing the article. Abstracts should include a description of the purpose, design, patients, results, and conclusions.

Letters to the Editor must be double-spaced and will be published at the discretion of the Editors. They may be edited for style and brevity. Those of a scientific nature may be subject to peer review. They should be no more than 500 words in length. Authors will be sent galley proofs before publication.

Letter of Transmittal

All authors must sign the letter of transmittal, with one author designated as correspondent and his or her name, address, and telephone number included.

The order of authorship is determined by the authors. All authors should meet the basic criteria for authorship (as stated below). Because order of authorship is assigned in different ways its meaning cannot be inferred accurately unless it is stated by the authors. Authors may wish to add an explanation of the order of authorship in a footnote. In deciding on order, authors should be aware that many journals limit the number of authors listed in the table of contents and that the National Library of Medicine lists in MEDLINE only the first 10 authors.

A letter of transmittal, except for one accompanying a manuscript from US Government employees whose work was done as part of their official duties, must include a paragraph that transfers copyright: "In consideration for reviewing and editing my submission, the author(s) undersigned hereby transfers, assigns, or otherwise conveys all copyright ownership to *The Western Journal of Medicine*, in the event that such work is published by the journal."

The letter of transmittal must include a statement of author responsibility: "I have participated in the conception and design of this work and in the writing of the manuscript and take public responsibility for it. I have reviewed the final version of the manuscript and approve it for publication. I attest to the validity and legitimacy of data in the manuscript and agree to be named as the lead author or coauthor of the manuscript."

The letter of transmittal must include a statement of financial disclosure: "I warrant that I have no financial interest in the drugs, devices, or procedures described in the enclosed manuscript (except as disclosed in the attached statement)."

Research or project support should be included as a footnote to the manuscript or the accompanying cover letter.

Manuscripts concerned with experimental investigation on human subjects must include in the text a statement that all subjects gave their informed consent and that approval of the appropriate ethics committee was obtained.

Acknowledgments

Acknowledgments will be printed on a select basis—to acknowledge those who contributed to but were not involved in the writing or review of the paper.

Preparation of Manuscripts

Everything, including references, tables, figure legends, and abstracts, **must be double-spaced.**

The original manuscript and two copies should be submitted on standard-sized heavy bond paper. Allow a margin of 2.5 to 4 cm (1 to 1.5 in) on both sides. Manuscripts transmitted by facsimile machine are not acceptable unless requested by the Editors.

All values should be in Système International (SI) units, with metric equivalents following in parentheses. Temperature readings should be given in Celsius. Use the generic name of drugs, with the salt or ester given when first used.

Figures (illustrations) should be submitted in triplicate in black and white, unmounted 12.7 × 17.8 cm (5 × 7 in) glossy prints, with the figure number, author's name, and top of the photo indicated with a label on the back. Patients (and relatives) have a right to anonymity in published clinical documentation. Details that might identify patients should be avoided unless essential for scientific purposes. Masking of the eye region in photographs of patients may be inadequate protection of anonymity. If identification of patients is unavoidable, informed consent should be obtained, and this should be clearly stated in the article. Changing data on patients should not be used as a way of securing anonymity. Figure legends, to be typed in sequence on the same page, should be in complete sentences. Any figures or tables previously published must be accompanied by a letter of permission to borrow from the copyright holder (the previous publisher). The permission of the authors should also be obtained. The Editors discourage the use of borrowed figures or tables.

All manuscripts will be subject to peer review to determine the originality, validity, and importance of content and conclusions. Reviewers' comments will be returned with rejected manuscripts at the discretion of the Editors. All reviewers will remain anonymous. Any conflict of interest, actual or potential, will have been revealed to the Editors.

All accepted manuscripts are subject to copy editing, and the corresponding author is sent edited galley proofs for approval and necessary minor changes. Excessive changes at this stage may result in a delay of publication or withdrawal of the paper. No changes will be made after the final, edited version has been approved by the corresponding author without notifying the author. It is the corresponding author's responsibility to clear all corrections and changes with his or her coauthors.

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References

All references should be cited in the text and listed in their order of citation. They should be pertinent to the text and not simply a listing of the results of a computerized search. They should be in *WJM* style per the examples given below.

(All references should be medical, scientific, or scholarly publications. Others—newspapers, magazines, etc—should be kept to a minimum and included in the text.)

Journal Articles

Abbreviations of journal titles should conform to those used in *Index Medicus*. List up to six authors; for seven or more, use et al after listing the first three.

1. Jones JS, Anderson HW Jr, Johnson DW, et al: The athletic heart revisited—Sudden death of a 28-year-old athlete. JAMA 1978; 292:444-456
2. Berman SM, Shah B, Wyle FA, Dacosta-Iyer M, McRae DM: Disseminated *Pneumocystis carinii* in a patient receiving aerosolized pentamidine prophylaxis. West J Med 1990; 153:82-86

Books

3. Berne EJ: Role playing in therapy, chap 2, Principles of Group Therapy. New York, NY, Oxford University Press, 1966, pp 35-51 (author of book is same as author of chapter)
4. Munsung JD: The role of drugs, chap 2, *In* Brest AN, Mayer JD (Eds): Hypertension—Vol 3, Therapy, 2nd Ed. Chicago, Ill, Year Book Medical Publishers, 1961, pp 456-479 (authors of book differ from chapter author)

Correspondence

5. Shusterman D: Espresso maker's wrist (Correspondence). West J Med 1990; 152:721-722

Government Publications

6. The Health Consequences of Smoking—Cardiovascular Disease: A Report of the Surgeon General. Washington, DC, US Dept of Health and Human Services publication No. (PHS) 84-50204, 1983
7. Centers for Disease Control: Update: Acquired immunodeficiency syndrome—United States. MMWR 1987; 36:522-526

Proceedings

8. O'Connell M: A Controlled Trial of Regional Intra-arterial FUDR Versus Systemic 5FU for the Treatment of Metastatic Colorectal Cancer Confined to the Liver. Presented at the annual meeting of the American Society of Clinical Oncology, San Francisco, December 1989

Mass Circulation Publications (Do not include in reference list; put in text)

(T. Harris, "Selenium-Rich Sediments Also Have Been Reported in Wildlife Refuges," *The Sacramento Bee*, September 8, 1985, p 5)

Personal Communications and Unpublished Data

This material should not be included in the reference list but should be given in parentheses in the body of the text, listing the person's name, highest academic degrees, and professional affiliation, whether the communication was oral or written, and the date (month and year).

Lyme disease has been reported in red squirrels (J. Sneed, PhD, Department of Wildlife, written communication, September 1990).

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(Continued from Page 240)

September 17—**Prozac: Serotenergic Reuptake Inhibitors.** Lutheran Medical Center, Wheat Ridge. Tues. Contact: Cary L. Walker, (303) 425-2009.

September 27-28—**Montrose Fall Clinics for Physicians.** Montrose Memorial Hospital, Montrose. Fri-Sat. Contact: Kathy Holman, (303) 240-7397.

October 7-11—**Family Practice Review,** University of Colorado School of Medicine, Denver. Mon-Fri. Contact: Joann Bauer, (303) 270-5195 or (800) 882-9153.

October 10-13—**Rural Perinatal Traineeship Program.** Children's Hospital, Denver. Thurs-Sun. Contact: Christine Sievers-Spencer, (303) 861-6413.

October 25-26—**14th Annual Perinatal Conference.** Children's Hospital of Denver at Laramie, Wyoming. Fri-Sat. Contact: Christine Sievers-Spencer, (303) 861-6413.

November 7-10—**Rural Perinatal Traineeship Program.** Children's Hospital, Denver. Thurs-Sun. Contact: Christine Sievers-Spencer, (303) 861-6413.

November 14—**Pre-term Infant Feeding Conference.** University of Colorado Health Sciences Center, Denver. Thurs. Contact: Trish Beachy or Nancy Briggs, (303) 270-7117.

November 22-23—**Colorado Springs Perinatal Conference.** Children's Hospital of Denver at Colorado Springs. Fri-Sat. Contact: Christine Sievers-Spencer, (303) 861-6413.

December 2-6—**Respiratory Therapy Traineeship Program.** Children's Hospital, Denver. Mon-Fri. Contact: Jeff Griebel, (303) 861-6188.

January 25-February 1—**15th Annual Infectious Diseases in Clinical Practice.** UCSF at Beaver Run Resort and Conference Center, Breckenridge. Sat-Sat. 24 hrs. Contact: UCSF.

First Wednesday of Each Month—**Various Topics in Neurology.** Sponsored by the Colorado Society of Clinical Neurologists. Contact: Colorado Society of Neurologists, (303) 449-3566.

CONTACT INFORMATION

U of Colo—Contact: University of Colorado School of Medicine, Office of Continuing Medical Education, 4200 E 9th Ave, Denver, CO. (303) 270-5195.

NEW MEXICO

Information, requests for accreditation, and items to be listed should be sent to the chair of the CME Committee, New Mexico Medical Society, 7770 Jefferson, Suite 400, Albuquerque, NM 87109, at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 828-0237.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

September 22-25—**Fourth Annual Southwest Regional Substance Abuse Conference: A Continuum of Care.** Holiday Inn Pyramid, Albuquerque. Contact: Marian Greher, 1479 Morning Glory NE, Albuquerque 87122. (505) 299-2266.

October 12-13—**Common Problems in Pediatric Nephrology.** Cloudcroft Lodge, Cloudcroft. Contact: Joe Dean, MD, 813 N Washington, Roswell 88201. (505) 622-2606.

November 1-3—**The 12 Lead ECG for the Primary Care Physician.** Presbyterian Hospital, Albuquerque. Contact: Jan Grieve, New Mexico Heart Clinic, 1001 Coal SE, Albuquerque 87106. (505) 242-2796 or (800) 888-6642.

November 8—**G.I. Update 1991.** Marriott Hotel, Albuquerque. Contact: Ann Winter, St Joseph Health Care Systems, 601 Grand NE, Albuquerque 87102. (505) 246-8004.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. Accredited institutions wishing to list AMA Category 1 CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, UT 84102; or phone (801) 355-5290. For information on CME accreditation, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution.

MEDICAL GRAND ROUNDS

Each Wed—8:00-9:00 a.m. Alternating between University of Utah Medical Center and VA Medical Center, Salt Lake City. Contact: William D. Odell, MD, PhD, Professor and Chairman, Dept of Internal Medicine, Univ of Utah, (801) 581-7606.

* * *

September 27-29—**Laser Surgery—Laparoscopic Cholesystectomy** (Sponsor: UUSM). Fri-Sun. The Laser Institute, University of Utah, Salt Lake City. Contact: (801) 581-7001.

November 15-16—**Laser Surgery—Laparoscopic Cholesystectomy** (Sponsor: UUSM). Fri-Sat. The Laser Institute, University of Utah, Salt Lake City. Contact: (801) 581-7001.

SPONSORS OF COURSES—ABBREVIATIONS

AHA: American Heart Association, Utah Affiliate, 645 E 400 South, Salt Lake City 84102. (801) 322-5601.

CH: Castleview Hospital (formerly Carbon Hospital), RFD 2, Box 46, Price 84501. (801) 637-4800.

HCH: Holy Cross Hospital, 1045 E First South, Salt Lake City 84102. (801) 350-4744.

ITS: Intermountain Thoracic Society, 1616 S 11th East, Salt Lake City 84105. (801) 484-4456.

LDSH: LDS Hospital, 8th Ave and "C" St, Salt Lake City 84143. (801) 321-1100.

LRH: Logan Regional Hospital, 1400 N 5th East, Logan 84321. (801) 752-2050.

MDH: McKay-Dee Hospital Center, 3939 Harrison Blvd, Ogden 84409. (801) 399-4141.

MVH: Mountain View Hospital, 1000 E Highway 6, Payson 84651. (801) 465-9201.

144: 144th Evacuation Hospital, PO Box 8000, Salt Lake City 84108. (801) 524-3924.

OSS: Ogden Surgical Society, PO Box 9311, Ogden 84409.

PVH: Pioneer Valley Hospital, 3460 S 4155 West, West Valley City 84120. (801) 968-9061.

UOS: Utah Ophthalmological Society, 540 E 500 South, Salt Lake City 84102. (801) 355-7477.

USH: Utah State Hospital, PO Box 270, Provo 84603-0270. (801) 373-4400.

UUSM: University of Utah School of Medicine, Office of Continuing Medical Education, 50 N Medical Dr, Salt Lake City 84132. (801) 581-8664.

VAMC: Veterans Administration Medical Center, 500 Foothill Dr, Salt Lake City 84148. (801) 582-1565.

VVMC: Valley View Medical Center, 595 S 75 East, Cedar City 84720. (801) 586-6587.

WRI: Western Rehabilitation Institute, 8074 S 1300 East, Sandy 84094. (801) 561-3400.

(Continued on Page 247)

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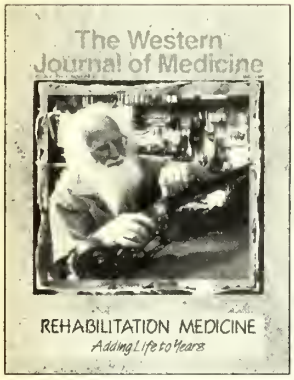

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MAY 1990

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- OVERVIEW OF ADDICTION MEDICINE *David Smith, Editor/Founder, Haight-Ashbury Free Clinic*
- CHEMICAL DEPENDENCE AND THE WORK PLACE *John Osterloh and Charles Becker*
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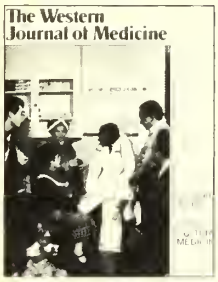

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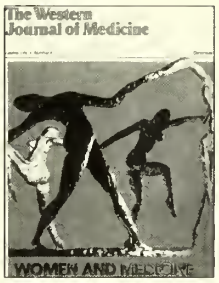

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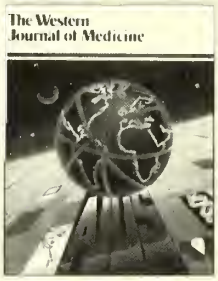

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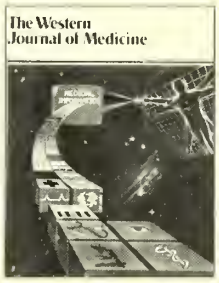

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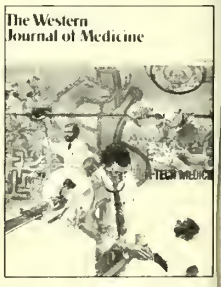

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(Continued from Page 244)

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Biomedical Science

Causes and Prevention of Calcium-containing Renal Calculi

ROGER A. L. SUTTON, DM, FRCP, FRCPC, *Vancouver, British Columbia*

Presented at the Plenary Session, Western Association of Physicians, Carmel, California, February 6, 1991.

Renal calculi are common; the lifetime risk for men in North America is about 20%, and the likelihood of a recurrence after the first stone is 50% at five years. It would be convenient to be able to predict which patients are going to have a stone recurrence when deciding how to investigate and treat them. A recent study from Sweden has examined this issue.[1] In this study, men in the population were screened at age 50 and again ten years later at age 60, with particular reference to their history of kidney stones, as well as many other aspects of their health. Factors that were associated with an increased likelihood of a recurrence in stone patients included a positive family history and an early age of the occurrence of stones. When a patient has stone disease start at age 25 compared with 45, or a positive family history, the likelihood of the recurrence of stones is approximately doubled.

Inhibitors and Promoters of Stone Formation

Natural inhibitors and promoters of crystal and stone formation exist in the urine; some of these are listed in Table 1. Magnesium, citrate, and glycosaminoglycans are naturally occurring inhibitors of oxalate stone formation. Two glycoproteins, nephrocalcin and Tamm-Horsfall protein, are probably extremely important inhibitors. Inhibition may occur at the level of crystal nucleation or growth, or the aggregation of crystals may be inhibited as they flow along the nephron.

Nephrocalcin, a glycoprotein identified some years ago,[2] is made in the proximal tubule and perhaps also in the loop of Henle. It contains γ-carboxyglutamic acid (as does osteocalcin). Nephrocalcin from the urine of stone formers and also from renal calculi may contain reduced quantities of γ-carboxyglutamic acid and be deficient in inhibitory action. Nephrocalcin is an inhibitor of both crystal growth and aggregation. Because of its fine caliber, the thin limb of the loop of Henle is probably an important site at which stone formation may begin. The deep portions of the loop of Henle are also characterized by some unusual physical conditions, including a high osmolality and high sodium and calcium concentrations. Nephrocalcin retains its inhibitory action in those unusual circumstances and hence may be effective in preventing stone formation in the thin loop of Henle.

TABLE 1.—*Naturally Occurring Inhibitors and Promoters of Calcium Oxalate Stone Formation*

Inhibitors
Pyrophosphate
Magnesium
Citrate
Glycosaminoglycans
Nephrocalcin
Tamm-Horsfall protein
Promoters
Urate
Tamm-Horsfall protein
? Cell membranes

TABLE 2.—*Risk Factors for Calcium Oxalate Stones*

Increased excretion of
Calcium, such as idiopathic hypercalciuria and primary hyperparathyroidism
Oxalate
Uric acid
Decreased excretion of
Volume
Citrate

The Tamm-Horsfall protein is normally excreted in urine in quantities of the order of 30 to 50 mg per day. Made exclusively in the thick ascending limb of the loop of Henle, it inhibits in a major way the aggregation of calcium oxalate crystals.[3] This effect is impaired under conditions of high sodium concentration and high osmolality because the Tamm-Horsfall protein tends to self-aggregate under those conditions.[4] This protein is added to the urine beyond the thin loop of Henle, where the conditions are such that it would self-aggregate. Its secretion at a more distal site in the nephron may allow it to function as an effective inhibitor of aggregation. It is possible that a high sodium intake and a high protein intake, both of which are known to promote stone formation, may impair the inhibitory action of Tamm-Horsfall protein by encouraging its self-aggregation. When self-aggregated, in fact, it may act as a promoter of stone formation.

Some of the known metabolic risk factors for calcium stones are shown in Table 2. Hyperuricosuria promotes calcium oxalate stone formation. Increasing uric acid concentration in vitro increases the precipitation of calcium oxalate from urine specimens.[5] The mechanism of this effect is still uncertain. Urinary citrate complexes calcium, rendering it unavailable for precipitation as calcium phosphate or calcium oxalate. A deficiency of citrate in the urine (hypocitraturia) is probably the major factor encouraging stone formation in patients with renal tubular acidosis and in patients being treated with acetazolamide. In addition, idiopathic calcium

(Sutton RAL: Causes and prevention of calcium-containing renal calculi. West J Med 1991 Sep; 155:249-252)

From the Department of Medicine, Division of Nephrology, University of British Columbia Faculty of Medicine, Vancouver.

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Reprint requests to Roger A. L. Sutton, DM, FRCP, FRCPC, Department of Medicine, University of British Columbia Faculty of Medicine, LSP-3, 910 W 10th Ave, Vancouver, BC, Canada V5Z 4E3.

TABLE 3.—*Clinical Presentation of Primary Hyperparathyroidism**

Presentation	Cases, % 1967 England	Cases, % 1990 Canada
Renal calculi	59	15
Osteitis fibrosa cystica	20	<5
Neither	21	>80

*Unpublished data.

oxalate stone formers frequently have subnormal urinary citrate excretions,[6] probably related to diet. A high protein intake, for example, induces a mild metabolic acidosis, the major known cause for the depression of urinary citrate excretion.

Primary Hyperparathyroidism as a Cause of Kidney Stones

Important causes of hypercalciuria include primary hyperparathyroidism and idiopathic hypercalciuria. The clinical presentation of primary hyperparathyroidism has changed in recent years (Table 3). Renal calculi used to be the most common clinical presentation, but less than 10% of patients now diagnosed as having primary hyperparathyroidism have urolithiasis. Twenty years ago, osteitis fibrosa cystica, the traditional cystic bone disease of primary hyperparathyroidism, was present in as much as 20% of cases, but now it is extremely rare, at least in North America. In a series from Paris, patients with osteitis fibrosa cystica were older and had poor nutritional vitamin D supplies, an unusual occurrence in North America because of the supplementation of dairy products with vitamin D (which is not usual in Europe.)[7] A recent study from New York compared patients with primary hyperparathyroidism presenting with or without renal stones.[8] Patients with stones tended to have more hypercalciuria (although not when it was expressed in relation to creatinine excretion) and somewhat higher excretion of urinary hydroxyproline. Hypercalciuria alone does not account for stone formation because the amount of urinary calcium excretion between patients with and without stones overlaps considerably. The clue to what may be contributing to stones in some patients with primary hyperparathyroidism may lie in an older study of crystal formation in urine.[9] These investigations determined the upper limit of metastability for calcium oxalate, the point at which crystals begin to form as the urine is increasingly saturated. The hyperparathyroid patients with stones were noted to have a much lower limit, that is, crystals formed at a lesser degree of supersaturation than in controls or in various other groups of stone patients. The simplest interpretation of this would be that there is an abnormal promoter of stone formation in the urine of patients with hyperparathyroidism and stones.

Idiopathic Hypercalciuria

In idiopathic hypercalciuria, patients excrete abnormally large amounts of calcium in the urine (>4 mg per kg per 24 hours), but plasma total and ionized calcium levels are normal. The pathophysiology of this disorder, the subject of controversy for many years, is still unclear (Table 4). Unresolved issues include whether the primary defect is an intestinal hyperabsorption of calcium or a renal tubular defect with calcium wasting and whether intestinal calcium hyperabsorption is or is not vitamin D-mediated. Other areas of considerable current interest are the role of the skeleton in idiopathic hypercalciuria and the role of dietary factors.

In patients with calcium stones, urinary sodium and urinary calcium excretions are strongly and positively correlated. In other words, a high urinary sodium excretion may contribute to the high calcium excretion. For a given increment in sodium excretion, stone patients tend to have greater increments in calcium excretion than do control subjects. Similarly, for a given increase in dietary protein (estimated from urinary urea excretion) men with calcium stone diathesis show a much steeper increase in urinary calcium excretion than do controls, a significant difference.[10] The same is true, although the differences are less significant, when women with stone formation are compared with suitable controls. There appears to be a hypersensitivity to the hypercalciuria-inducing effect of dietary protein in patients with stone diathesis. Restricting dietary protein is therefore increasingly becoming a mode of therapy to try to prevent calcium oxalate calculi. Whether this hypercalciuric effect of ingested protein is on the skeleton, on the renal tubule, or even in the gut has not yet been clarified.

In idiopathic hypercalciuria, whatever its pathogenesis, intestinal calcium is hyperabsorbed. The mean serum calcitriol level in hypercalciuric stone formers is greater than in normal controls but not sufficiently so to explain the observed calcium hyperabsorption. Other mechanisms that might promote calcium absorption in these patients are therefore being sought. In a recent study, calcium-magnesium-adenosine triphosphatase activity in erythrocytes from hypercalciuric patients was found to be significantly higher than in controls.[11] Furthermore, this erythrocytic enzyme activity was positively correlated with the excretory rate of urinary calcium. This might suggest the presence of a generalized abnormality of calcium transport in idiopathic hypercalciuria affecting cell membranes other than those of the gut and the kidney. A rat model of idiopathic hypercalciuria has been obtained by selective breeding for hypercalciuria.[12] In this model the hypercalciuria is clearly not vitamin D-mediated in that the serum calcitriol levels of these exceedingly hypercalciuric rats with greatly increased rates of calcium absorption are not different from those of the controls. The fact that calcitriol levels are not suppressed in the hypercalciuric rats could indicate a subtle defect in its metabolism, but the problem is not simply one of overproduction of calcitriol.

Conventional metabolic balance studies usually show an overall negative calcium balance in patients with idiopathic hypercalciuria. This suggests that skeletal resorption may be contributing to the hypercalciuria. Furthermore, a decrease in bone density, particularly that of trabecular bone, and an

TABLE 4.—*Abnormalities Described in Idiopathic Hypercalciuria*

- Absorptive hypercalciuria
- Renal leak of calcium with secondary hyperabsorption
- Increased sensitivity to the hypercalciuric effect of
  - Dietary sodium
  - Dietary protein
- Increased calcium-magnesium-ATPase activity (erythrocytes)
- Increased skeletal turnover
- Increased interleukin-1 (in monocytes)

ATPase = adenosine triphosphatase

increase in urinary hydroxyproline have been reported. For example, we measured urinary hydroxyproline levels in three 8-hour periods during the day in stone formers and in normal subjects and observed that, especially during the daytime hours, the urinary hydroxyproline levels were higher in patients than in controls.[13] Patients and controls were on gelatin-free diets, so the urinary hydroxyproline was presumed to reflect endogenous bone turnover. We interpreted these results to suggest that in patients with stone, the normal slowing of bone resorption during the daytime, when calcium is being ingested, may not occur.

Interleukin-I activity has been determined in circulating peripheral monocytes in stone patients and controls.[14] Patients who were stone formers were divided into those with fasting hypercalciuria (a high calcium excretion after an overnight fast, probably in part due to increased skeletal resorption) and those with absorptive hypercalciuria who did not have increased calcium excretion after a fast but did hyperabsorb ingested calcium. The remaining patients had normal urinary calcium excretion. The mean interleukin-1 activity in the cultured peripheral monocytes was greatly increased in patients with fasting hypercalciuria, although there was some overlap with the controls. These data suggest that increased interleukin-1 production by circulating monocytes (which are related to osteoclasts in the bone) might be the mechanism of increased bone resorption in idiopathic hypercalciuria. Patients with fasting hypercalciuria also had a reduced trabecular bone density (determined by computed tomography) and an increased urinary excretion of hydroxyproline in comparison with the other two groups.

In the treatment of idiopathic hypercalciuria, some dietary factors to which attention should initially be directed, notably high dietary salt and protein, have already been mentioned. Thiazide diuretics, which are effective in reducing stone recurrences,[15] lower urinary calcium levels by enhancing calcium reabsorption by the distal renal tubule. Over time the use of thiazides may also cause an increase in bone density as evidenced by both formal bone density measurements in the spine and the limbs[14,16] and by a reduced incidence of hip fractures.[17]

Abnormalities in Oxalate Metabolism

Calcium oxalate is the most frequent crystalloid component of kidney stones. Oxalic acid, named after the plant wood sorrel, or *Oxalis*, is an end product of metabolism in vertebrates. Vertebrates lack enzymes to metabolize oxalate further, and this simple molecule has no known role in mammalian physiology. Recently a chloride-oxalate exchanger has been demonstrated on the brush border of cells of the proximal renal tubule,[18] in addition to the chloride-formate exchanger that had previously been identified.[19] It is possible that the oxalate-chloride exchanger might have a role in the reabsorption of sodium chloride in the proximal tubule. Alternatively, it may simply be involved in the oxalate secretory process that is known to occur along the nephron.

Oxalate's clinical importance relates only to the extreme insolubility in water of its calcium salt. At less than 0.1 mmol per liter, it is much less soluble than, for example, calcium phosphate or calcium carbonate. The process of crystal or stone formation in the urinary tract has long been thought to be related to supersaturation of the urine with insoluble urinary constituents. The saturation of a solution with respect to calcium oxalate can be considered in relation to the behavior of calcium oxalate seed crystals added to the solution. In a supersaturated solution, the crystals will tend to grow, whereas in an unsaturated solution they will tend to dissolve. The formation product is the degree of supersaturation at which spontaneous crystal formation occurs.

A modest increase in urinary oxalate levels may actually be more important than a proportionately similar increase in urinary calcium as a risk factor for calcium oxalate stones. Urinary oxalate is unbound, whereas urinary calcium is partially chelated by citrate. Another reason may be the high molar ratio of calcium to oxalate in the urine. Mild hyperoxaluria may occur in as much as 40% of patients in whom idiopathic calcium oxalate stones form, often along with other metabolic abnormalities such as hypercalciuria. Occasionally a high dietary oxalate may be responsible for hyperoxaluria. In a study carried out in Saudi Arabia, hyperoxaluria was frequently found in stone-forming patients and was thought to result from unusually low dietary calcium intakes, which may enhance the absorption of dietary oxalate.[20] This observation has led to the introduction of calcium citrate as a mode of therapy in such patients.[20] We have identified a few patients of this type in Vancouver and are treating them similarly. This condition is analogous to enteric hyperoxaluria, but the patients have no evidence of bowel disease.

The precise enzyme defect in severe type 1 primary hyperoxaluria has recently been identified,[21] and efforts are now being made to determine whether idiopathic mild hyperoxaluria could be due, in some patients, to a minor abnormality of this enzyme. This seems unlikely, however, because urinary glycolate levels, which are increased along with oxalate in type 1 hereditary hyperoxaluria, are usually not increased in patients with mild idiopathic hyperoxaluria. Finally, some patients may have a renal oxalate transport defect, which could be a manifestation of a generalized oxalate transport defect in stone formers. The exchange of labeled oxalate across erythrocyte membranes has been reported to be greatly increased in idiopathic calcium stone formers when compared with controls or with other patients.[22] It was proposed that this might reflect an abnormality in membrane permeability to oxalate that might also affect oxalate transport in the gut and the kidneys. Interestingly, this defect in the erythrocytes was corrected with the use of thiazide diuretics, but the nature of the defect remains unclear.

The treatment of mild idiopathic hyperoxaluria is unlikely to be entirely satisfactory until the pathophysiology is understood. The use of calcium in enteric hyperoxaluria has already been mentioned. An alternative may be compounds such as complex organic alginates that adsorb oxalate in the gut lumen and inhibit its absorption from the diet.[23] Patients with type 1 primary hyperoxaluria may respond to a regimen of pyridoxine hydrochloride, and some patients have received a liver transplant with reversal of the metabolic abnormality. Pyridoxine may have a place in the treatment of the mild idiopathic form, but results have generally not been encouraging. Finally, we can speculate about the possibility of gene therapy for the treatment of hyperoxaluria. As mentioned earlier, vertebrates cannot metabolize oxalate further, but some bacteria possess an oxalate decarboxylase. Conceivably it might be possible to use such an enzyme to degrade oxalate in higher animals. I am indebted to A. B. Peck, MD, and colleagues of Gainesville, Florida, for allowing me

to present some as-yet-unpublished material.[24] These investigators have cloned the oxalate decarboxylase enzyme from the bacterium *Oxalobacter formigenes*, and they have recently succeeded in expressing it in *Escherichia coli*, thus conferring the ability on this species to convert oxalate to formate. The next step would be to transfer this enzyme into a mammalian cell and possibly one day use it to treat severe human hyperoxaluric disorders.

Summary

Kidney stones are common, and recurrences are the rule. At least 90% of patients with kidney stones probably have some identifiable metabolic risk factor. Effective prophylaxis is often available, but with the relatively low rate of recurrence, compliance with the treatment may be a problem. Studies are required to determine the cost-effectiveness of metabolic investigation and prophylactic therapy versus the possible need for repeated treatment by means of extracorporeal lithotripsy, especially in patients having a first calcium oxalate stone.

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Articles

Angiographic Yield in Penetrating Extremity Trauma

VERNON HENDERSON, MD; RAMAN NAMBISAN, MD; MICHAEL E. SMITH, MD;
KENNETH K. YIM, MD; *and* CLAUDE H. ORGAN, JR, MD, *Oakland, California*

Indications for angiography in the evaluation of penetrating extremity trauma remain controversial. Our experience was reviewed to determine the yield of angiography in penetrating extremity trauma and to correlate clinical findings with angiographic results. During an 81-month period from 1983 through 1989, 284 extremity arteriograms were carried out in 268 patients. The angiographic yield in patients with abnormal clinical findings was 51%. The angiographic yield in patients when proximity of the injury to major vessels was the only indication was 6% (7% with gunshot wounds and 0% with stab wounds). Neurologic deficit alone as an indication for angiography accounted for 55% of the angiograms interpreted as "negative" and none of those interpreted as "positive." We conclude that the use of angiography in patients with gunshot wounds to the extremity with "proximity injuries" to major vessels should continue, its use is not warranted in extremity stab wounds when proximity is the sole indication, and abnormal neurologic findings in the absence of other findings are a poor predictor of vascular injury.

(Henderson V, Nambisan R, Smith ME, Yim KK, Organ CH Jr: Angiographic yield in penetrating extremity trauma. West J Med 1991 Sep; 155: 253-255)

Angiography is used with increasing frequency in the evaluation of suspected vascular injuries from penetrating trauma. The routine use of angiography in the absence of specific clinical findings has been seriously questioned in recent reports, which recommended limiting its use to selected patients as safe and cost-effective.[1-8] Specific clinical findings such as pulse deficit, bruit, expanding hematoma, arterial bleeding, and neurologic deficit are widely accepted indications for angiography in patients with penetrating extremity trauma.[9-11] Controversy concerning the aggressive use of angiography continues, however, when an injury's proximity to major vessels is the only indication.[11-13] The experience at the Highland General Hospital Trauma Center, Oakland, California, was retrospectively reviewed to determine the yield of angiography in penetrating extremity trauma and to correlate clinical findings with angiography results.

Patients and Methods

The records of patients admitted to the Highland General Hospital Trauma Center who underwent angiography because of penetrating extremity injuries were retrospectively reviewed for the period beginning January 1, 1983, and ending September 1, 1989. All patients were evaluated initially by the chief surgical resident or the attending surgeon. Excluded from this review were patients with definite vascular injuries who were operated on based solely on clinical indications and patients with concomitant injuries requiring emergency operations. The decision for angiography was made by attending surgeons or the chief surgical resident after consultation with the attending surgeon. Conventional arteriography was done by interventional radiologists using standard catheter techniques with serial filming. Results were jointly interpreted by the radiologist and the attending surgeon.* Decisions for surgical exploration of these vascular injuries were based on a combination of clinical and angiographic findings.

The clinical findings used in the decision-making process were diminished or absent distal pulses, a palpable thrill or bruit, cold or cyanotic extremities, a neurologic deficit, arterial bleeding, or an expanding hematoma.[9-11] The angiographic findings interpreted as "positive" include occlusion of a major vessel, an arteriovenous fistula, an intimal injury, pseudoaneurysm, the extravasation of contrast material, and spasm. Muscular branch lacerations were not considered positive angiographic findings. All operative reports were reviewed, and follow-up information was recorded from outpatient records.

Results

During this 81-month period, a total of 284 angiographic procedures were carried out in 268 patients for penetrating extremity trauma with vascular proximity. Their ages ranged from 15 to 59 years, with a male to female ratio of 12:1 (247 men and 21 women). Most of the injuries were gunshot wounds (79%), and 21% were stab wounds. Two thirds (142 of 213) of the gunshot wounds involved the lower limbs, and a third were in the upper extremities. Of the 55 stab wounds encountered, 32 (58%) and 23 (42%) involved the upper and lower extremity, respectively. Upper extremity angiographic procedures were done in 39% of the patients and 61% in the lower extremities. Of all studies, 229 (81%) were performed for gunshot wounds and 55 (19%) for stab wounds. Of the 284 arteriograms, the results of 57 (20%) were positive based on the aforementioned criteria; 44 of 229 (19%) in gunshot wounds, and 13 of 55 (24%) in stab wounds. A total of 194 angiograms (68%) were done because of proximity of the injury to major blood vessels (70% of the gunshot wounds and 62% of the stab wounds).

The angiography yield was 6% (11 of 194) when penetrating extremity trauma with proximity was the only indication;

*Arthur T. Gronner, MD, of the Radiology Department provided assistance.

From the Department of Surgery, University of California, Davis-East Bay, Oakland.
Reprint requests to Claude H. Organ, Jr, MD, Department of Surgery, University of California, Davis-East Bay, 1411 E 31st St, Oakland, CA 94602.

in the gunshot and stab wound groups, the yield was 7% (11 of 160) and 0% (0 of 34 [95% confidence interval, 0% to 10%]), respectively.

Of the 11 patients with positive angiograms, 5 had potentially serious injuries, 3 of which were confirmed during an operation. These included a superficial femoral artery occlusion requiring vein grafting, a femoral arteriovenous fistula managed by resection and a polytetrafluoroethylene graft replacement, a superficial femoral vein injury treated by ligation, partial occlusion of the right radial artery with good collateral flow, and thrombosis of the anterior tibial artery with intact posterior tibial and peroneal arteries. The last two patients were observed clinically and subsequently discharged. The remaining six patients with angiograms showing spasm were observed and discharged without additional clinical signs or symptoms developing. All nonoperated patients had an uneventful hospital course (Table 1).

One angiogram falsely interpreted as "negative" occurred in a patient with a gunshot wound to the right thigh who later presented with a pseudoaneurysm of the superficial femoral artery that was successfully repaired. He suffered another gunshot wound to the same extremity; angiography revealed patent vessels and no abnormalities.

A definition of yield determinations is given in Table 2. The criteria for positive clinical findings were based on previous reports.[9-11] To determine the importance of each clinical finding, the predominant clinical finding in each patient was correlated with angiographic results. There were 24 negative angiograms when only a neurologic deficit was the indication for angiography. This group represented 55% of all negative angiograms.

Discussion

The role of angiography in the evaluation of penetrating trauma to the extremities remains controversial, particularly in patients who have no indicative clinical findings other than proximity of the injury to major vessels.[11-13] The published yield of positive angiograms in this set of patients (proximity) from recent studies varies between 6% and 21%.[1,4-7,13] The positive angiography yield at the Highland General Hospital Trauma Center for this group of patients was 6%. All positive angiograms were in the group sustaining gunshot wounds, and none were observed in the stab wound group. The yield is actually 7% in patients with gunshot wounds and 0% in patients with stab wounds.

Of the patients in this series, 68% underwent angiography because of proximity of injury to blood vessels—70% of the patients with gunshot wounds and 62% of those with stab wounds. These figures are consistent with those of previous reports.[5,6,10] The overall yield of 6% is also in agreement with the 6% to 21% published yield.[11]

TABLE 1.—*Location of Positive Angiographic Findings With Normal Clinical Findings (False-Negative)*

Angiographic Finding	*Patients, No.*	*Treatment*
Superior femoral artery occlusion	1	Vein graft
Superior femoral AV fistula	1	Resection, Gortex graft
Superior femoral vein laceration	1	Ligation
Contusion of radial artery	1	Observed and discharged
Laceration of anterior tibial artery	1	Observed and discharged
Spasm of popliteal artery	2	Observed and discharged
Spasm of deep femoral artery	2	Observed and discharged
Spasm of brachial artery	2	Observed and discharged

AV = arteriovenous

TABLE 2.—*Angiography Versus Clinical Findings (n = 284)*

Physical Findings	*Angiography*	*Gunshot Wounds, Patients, No.*	*Stab Wounds, Patients, No.*
Abnormal	Positive	33	13
Abnormal	Negative	36	8
Normal	Positive	11	0
Normal	Negative	149	34

Only three patients without clinical findings were operated on based on angiographic findings. (Management change as a consequence of angiography in patients with no clinical findings is 1.5%, or 3 of 194 patients.) It is easy to argue that patient management is rarely changed by doing angiograms when no clinical finding is present. Unfortunately, the follow-up in this group of patients is often unreliable. The outcome of patients with positive angiography, but not operated on, based on clinical judgment remains unknown. It is safer to manage a known injury selectively based on clinical judgment than to be later surprised by a potentially dangerous occult injury.

The mechanisms of vascular injury due to gunshot and stab wounds are somewhat different. Stab wounds usually cause direct trauma to the vascular structure with minimal surrounding tissue damage. Bullets can be of high velocity and energy, and, in addition to the resulting direct trauma, the temporary cavity that follows can cause considerable damage at a distance greater than the diameter of the missile tract, resulting in vascular injury away from the wound site with accompanying surrounding tissue damage.[14,15]

The use of angiography in patients with no clinical findings must be balanced against the complications of angiography itself. No patient in this series had a major complication from angiography. The overall major complication rate from angiographic procedures performed on trauma patients during this period was 0.6%, consistent with the published results of less than 1%.[16] Although the chance of major complication is small, serious potential risks certainly exist.

We concur that the use of angiography in patients with gunshot wounds to the extremity with major vessel proximity is appropriate because of the 7% yield. The greater potential for distant vascular injuries from the destructive force of missiles outweighs the risks of complications. In patients with stab wounds to extremities and absent clinical findings, angiography is not warranted. This confirms previous recommendations by Hartling and co-workers.[11]

The yield of angiography in patients with definite clinical findings was 51% (46 of 90) for both groups: 48% (33 of 69) in the gunshot wound group and 62% (13 of 21) in the stab wound group. Physical examination, in our experience, is sensitive in identifying vascular injuries, as indicated by other reports.[6,7,10,11]

The correlation between clinical findings and angiographic results showed that the most reliable signs were a pulse deficit, active bleeding, or an expanding hematoma. These accounted for 63% of the positive angiograms and only 18% of the negative angiograms. A neurologic deficit alone as an indication accounted for more than half (55%) of the negative angiograms; there were no positive angiograms in this group. This is in agreement with the findings of O'Gorman and associates[5] but differs from other reports that

showed that a neurologic deficit alone as an indication accounted for 11% to 42% of positive angiograms.[6,9,10] The number of patients with an isolated neurologic deficit as an indication for angiography in these series was small. The total number in all three series consisted of 9 positive angiograms in 30 patients with a neurologic deficit alone as the indication for angiography. Clearly a neurologic deficit is a vague and broad term. It can mean a variety of symptoms ranging from numbness or tingling to paralysis. Paralysis is a well-known sign of acute arterial vascular insufficiency.[17] A number of reasons for paresthesia may exist in an extremity distal to a penetrating injury, however. Neurologic deficit was defined in only one series as simply motor or sensory loss.[9]

Our experience supports the continued use of angiography in extremity gunshot wounds with proximity to a major blood vessel. The use of angiography for stab wounds based solely on proximity to vessels should be abandoned. Abnormal neurologic findings in the absence of other findings are a poor predictor of vascular injury. Patients managed by physical findings alone and those with injuries managed by observation need to be observed carefully after an injury because the long-term natural history of these injuries is unknown.

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Articles

Leg Symptoms in Outpatient Veterans

SYLVIA K. OBOLER, MD; ALLAN V. PROCHAZKA, MD, MSc; *and* THOMAS J. MEYER, MD; *Denver, Colorado*

In a survey of outpatients at the Denver Veterans Affairs Medical Center for common leg symptoms—515 questionnaires returned in a 3-week period—56% reported nocturnal leg cramps, 29% reported the restless leg syndrome, and 49% reported symptoms of peripheral neuropathy. Only 33% of patients had no symptoms relating to their legs. Patients often did not report these symptoms to their physician but were more likely to do so if the symptoms were frequent. Conditions especially related to leg symptoms were hypertension, peripheral vascular disease, coronary artery disease, cerebrovascular disease, kidney disease, and hypokalemia. Most patients did not receive effective therapy for these symptoms.

(Oboler SK, Prochazka AV, Meyer TJ: Leg symptoms in outpatient veterans. West J Med 1991 Sep; 155:256-259)

Several leg symptoms commonly seen in a primary care practice have never been adequately studied. Textbook statements that nocturnal leg cramps occur in about 15% of healthy young adults[1(p1215)] and as many as 70% of patients older than 50 years [2(pp300-301)] are not referenced. Nocturnal leg cramps are painful, involuntary contractions of muscles occurring at rest and causing a visible, palpable knot in a muscle, usually the gastrocnemius or soleus.[3] Pemberton reported in 1935 that 41% of arthritis patients had nocturnal leg cramps.[4] There have been no prevalence studies on general medicine clinic patients. Nocturnal leg cramps result from motor unit hyperactivity due to a variety of causes such as hemodialysis, lower motor neuron disease, electrolyte imbalance, and drugs.[5-10] Relief of these cramps requires stretching the contracted muscle, usually through passive dorsiflexion of the foot. Initial physical measures to prevent nocturnal leg cramps include calf stretching exercises and sleeping positions that minimize foot plantar flexion.[11,12] When these measures fail, various drug regimens have been suggested. Since 1940, quinine sulfate has been used to relieve night cramps.[13] Small double-blind studies have shown quinine superior to placebo in reducing the frequency and severity of leg cramps in elderly[14,15] and hemodialysis[16] patients but not in medical inpatients.[17] Other drugs whose use has been recommended but without good evidence of efficacy include verapamil, diazepam, diphenhydramine hydrochloride, phenytoin, dantrolene, procainamide hydrochloride, imipramine hydrochloride, and vitamin E.[18-20]

Ekbom renewed interest in a common but virtually ignored condition, the restless legs syndrome.[21] This is a clinical diagnosis based on the presence of peculiar creeping or crawling sensations, usually in the lower leg, felt deep inside the muscle or bones, occurring at rest and relieved by motion or exercise.[22] The restless legs syndrome is said to be less common than nocturnal leg cramps, again without supporting data, but does occur in 11% of insomnia patients.[23] The restless legs syndrome has been variously reported in 5% of healthy normal subjects,[21] 15% of surgical outpatients,[24] and 15% to 20% of dialysis patients.[25] Theories for the cause of the restless legs syndrome have included heredity, iron deficiency, uremia, pregnancy, anxiety or depression, and a variety of other causes.[21,22,26] Suggestions for treatment have included the use of iron, vasodilators, propranolol hydrochloride, clonidine, baclofen, carbamazepine, clonazepam, and dopaminergic agents, and transcutaneous electric nerve stimulation.[27-31]

Peripheral neuropathy symptoms, especially due to diabetes mellitus, are common in an older population, but their prevalence in a primary care population has never been reported. Peripheral neuropathy is characterized by dysesthesias in the extremities, most often numbness and tingling or pain in the feet and lower legs.[32(p1509)] The long list of nerve-damaging processes resulting in these symptoms includes metabolic processes, particularly diabetes and vitamin deficiencies, toxins such as alcohol, antimicrobial or chemotherapeutic drugs, environmental chemicals, inflammatory diseases, neoplasms, and hereditary neuropathies. While several studies have examined the causes of neuropathy within specific patient groups, including the elderly,[33] inpatients in an Indian general hospital,[34] and patients referred to the Mayo Clinic with neuropathy of unknown cause,[35] the prevalence of peripheral neuropathy symptoms or dysesthesias in the primary care population has not been evaluated. Even among diabetic patients, "the incidence of neurological deficit in diabetes mellitus is not known."[36(p977)] Brown and coworkers estimated that 10% of all diabetic patients have symptomatic neuropathy,[37] but Clements reported signs and symptoms of polyneuropathy in half of all patients with diabetes observed for more than 20 years.[38] Recommendations for the treatment of both pain and paresthesias of peripheral neuropathy have been based on small series, mainly in diabetic patients, and have included the use of phenytoin, carbamazepine, amitriptyline hydrochloride, fluphenazine hydrochloride, and recently mexiletine hydrochloride.[39-43]

Because the causes of these nonfatal but often aggravating conditions are so poorly understood, recommendations for their treatment are largely empiric. We therefore studied patients at the Denver (Colorado) Veterans Affairs Medical Center (VAMC) to answer two questions: What is the prevalence of nocturnal leg cramps, the restless legs syndrome, and symptomatic peripheral neuropathy in an outpatient veteran population? What treatment regimens for these symptoms have been attempted, and which did the patients report most successful?

From the Ambulatory Care Service, Veterans Affairs Medical Center, Denver, Colorado, and the Department of Medicine, University of Colorado Health Sciences Center, Denver.

Reprint requests to Thomas J. Meyer, MD, Ambulatory Care Service, VA Medical Center (11B), 1055 Clermont St, Denver, CO 80220.

Methods

We developed a two-page questionnaire for anonymous self-administration at the Denver VAMC. A patient's age and sex, clinic appointment, and underlying self-reported medical conditions including the presence of diabetes mellitus, hypertension, peripheral vascular disease, coronary artery disease, previous stroke, kidney failure, hypokalemia, and hypocalcemia were recorded. These associated conditions were selected from several reviews on the subject. Patients were asked about the presence and, if present, the frequency of symptoms, whether their physicians had been told of the symptoms, which drugs had been tried, and which worked best. The identifying questions for individual symptoms were as follows:

- For nocturnal leg cramps: Have you had trouble with cramps in your calves or feet at night?
- For the restless legs syndrome: Have you had trouble with restless or crawling sensations in your legs at night?
- For peripheral neuropathy: Have you had trouble with numbness or tingling in your legs or feet?

The study was approved by the Human Subjects Committee of the Denver VAMC. For each symptom, the patient was asked to circle any drugs that had been tried and then to specify which drug worked best. For cramps, the drugs listed were quinine, vitamin E, phenytoin, diazepam, procainamide, amitriptyline, diphenhydramine, and other (please specify). For restless legs, the drugs were iron, diazepam, clonazepam, amitriptyline, and other. For peripheral neuropathy, the choices were phenytoin, carbamazepine, amitriptyline, and other.

The primary care clinics at the Denver VAMC are staffed by general internal medicine faculty, internal medicine residents, and nurse practitioners. Over a three-week period the questionnaire was distributed to all patients attending the primary care, internal medicine, diabetes, hypertension, and geriatric clinics. The questionnaire was given to the patients by the nurse at clinic check-in, filled out while the patients were waiting for appointments, and collected by the primary care givers at the appointment.

Data analysis using the SPSS/PC [Statistical Package for the Social Sciences for use on a personal computer] program[44] centered on the frequency of the various leg symptoms according to demographic factors and reported chronic disease. Estimates of prevalence are reported with 95% confidence limits to provide an indication of the precision of our estimates. Odds ratio confidence limits were calculated using Miettinen's method.[45] χ^2 Tests without correction for continuity were used to test statistical significance.

Results

The self-administered questionnaire was distributed to 604 consecutive patients. Of these, 515 were returned, for a response rate of 85%. Because not all patients answered all questions, denominators may vary in the analyses. Of the respondents, 95% were men, with a mean age of 60.4 years (range, 26 to 91). Chronic medical conditions reported by the patients included hypertension (35%), coronary artery disease (25%), diabetes mellitus (24%), peripheral vascular disease (20%), previous cerebrovascular accident (8%), history of hypokalemia (14%), kidney disease (2%), and history of hypocalcemia (2%).

TABLE 1.—*Prevalence of Leg Symptoms*

Symptom	Patients, No./Total*	%	95% Confidence Interval, %
Nocturnal leg cramps	276/490	56	52 to 61
Restless legs syndrome	132/453	29	25 to 33
Peripheral neuropathy	234/477	49	45 to 54
None of the 3	140/430	33	28 to 37
All of the 3	90/430	21	17 to 25

*The total number of patients responding who had the symptom versus the number who answered the question. The denominators vary because not all patients answered all questions.

The prevalence of the three leg symptoms is shown in Table 1.

Associations of the three symptoms with self-reported chronic disease are shown in Table 2. Unexpectedly, diabetes mellitus was not correlated with any of these symptoms. Peripheral vascular disease was associated with all three symptoms ($P < .001$). Hypertension, stroke, and kidney failure were associated with neuropathy symptoms, and leg cramps were associated with coronary artery disease.

Table 3 shows how frequently patients experience these leg symptoms. The frequency of symptoms strongly correlates with patients' reporting symptoms to physicians (Table 4). Of 64 patients with daily leg cramps, 52 (82%) had told their physician, while of 60 patients with 1 to 12 episodes per year, only 22 (37%) reported them. Of 276 patients with leg cramps, 213 answered questions regarding treatment and 77 (36%) reported some sort of drug treatment. Of those with daily cramps, 42 (55%) had received treatment. Quinine sulfate was used in 34 patients, followed by diazepam in 17, vitamin E in 12, amitriptyline in 10, phenytoin in 9, and diphenhydramine in 8. Some patients received more than one drug. Quinine was reported to be most effective in 50% of those receiving it. None of the other drugs were described as effective.

TABLE 2.—*Association of Leg Symptoms With Chronic Disease*

Disease	Odds Ratio	95% Confidence Interval	P
Nocturnal Leg Cramps			
Peripheral vascular disease	3.49	2.11 to 5.76	.0001
Hypokalemia	1.74	1.01 to 3.01	.047
Coronary artery disease	1.68	1.10 to 2.56	.015
Hypertension	1.35	0.92 to 1.97	.121
Kidney disease	1.83	0.48 to 7.02	.378
Stroke	1.07	0.55 to 2.06	.8392
Diabetes mellitus	0.99	0.75 to 1.29	.9421
Hypocalcemia	1.03	0.27 to 3.86	.9650
Restless Legs			
Peripheral vascular disease	3.17	1.98 to 5.07	.0001
Hypocalcemia	6.18	1.44 to 26.46	.0141
Hypertension	1.54	1.02 to 2.34	.0421
Coronary artery disease	1.58	1.01 to 2.48	.0465
Hypokalemia	1.56	0.88 to 2.77	.1295
Kidney disease	2.44	0.63 to 9.51	.1986
Stroke	0.78	0.35 to 1.73	.5401
Diabetes mellitus	1.11	0.69 to 1.78	.6664
Peripheral Neuropathy Symptoms			
Peripheral vascular disease	5.07	3.07 to 8.37	.0001
Stroke	3.48	1.67 to 7.25	.0016
Kidney disease	9.52	1.73 to 52.35	.0096
Hypertension	1.62	1.11 to 2.37	.0130
Hypocalcemia	6.26	0.97 to 40.23	.0533
Hypokalemia	1.62	0.96 to 2.73	.0705
Coronary artery disease	1.41	0.93 to 2.14	.1048
Diabetes mellitus	1.24	0.81 to 1.90	.3217

TABLE 3.—*Frequency of Leg Symptoms*

Frequency	Patients, No. (%) Nocturnal Leg Cramps	Restless Legs Syndrome	Peripheral Neuropathy*
1-12/yr	60 (23)	14 (11)	28 (13)
1-3/mo	71 (27)	28 (22)	31 (14)
1-4/wk	67 (26)	33 (26)	45 (21)
Daily	64 (24)	54 (42)	115 (53)
Total	262	125	219

*Includes dysesthesia symptoms.

TABLE 4.—*Patients Reporting to Physicians According to Frequency of Symptoms*

Frequency of Symptom	Patients, %* Nocturnal Leg Cramps	Restless Legs Syndrome	Peripheral Neuropathy†
1-12/yr	37	21	31
1-3/mo	51	48	42
1-4/wk	63	70	68
Daily	82	68	78

*Association between frequency of symptoms and reporting to physician (χ^2 test), $P < .01$.
†Includes dysesthesia symptoms.

Although 70% of patients with frequent restless legs reported it to their physicians, only 29 of 104 (28%) patients reported receiving drugs. Diazepam was used in 16 patients, followed by amitriptyline in 9, iron in 5, and clonazepam in 3. None of these were reported by the patients as being particularly helpful.

More patients with numbness and tingling than with the other leg symptoms reported that their symptoms occurred daily (53% of 219), but still only 78% had discussed it with their physicians. Even fewer of them reported receiving treatment. Of 178 patients with dysesthesias who responded to treatment questions, only 34 (19%) of the total and 21% of those with daily symptoms reported receiving drug therapy. Of these, 14 had received phenytoin, 13 had received amitriptyline, 3 remembered having received carbamazepine, and 1 each was given chlordiazepoxide, quinine, tolmetin, and acetaminophen plus codeine. Only ten identified a drug as being effective—phenytoin in four, amitriptyline in two, and one each for carbamazepine, chlordiazepoxide, quinine, and acetaminophen plus codeine. Seven patients specifically wrote that no drug treatment worked.

Table 5 shows the percentage of patients with one of eight self-reported diagnoses who had each of the leg symptoms alone or in combination. The restless legs syndrome rarely occurred alone. The combination of cramps and neuropathy was about as common as cramps alone. A surprisingly high number of patients had all three symptoms. Among patients with hypertension, 29% reported no leg symptoms and 28% reported all three symptoms of cramps, restless legs, and the dysesthesias of peripheral neuropathy. In diabetic patients surveyed, 29% had no symptoms and 23% had all three symptoms, while 14% reported dysesthesias alone, 10% reported cramps and dysesthesias, and 3% reported both restless legs and dysesthesias. Almost half the patients with peripheral vascular disease reported all three symptoms.

Discussion

In a recent review it was noted that the actual incidence of muscle cramps in internal medicine practices is unknown.[46] We have found that 56% of a veteran outpatient population experiences nocturnal leg cramps, with 12% reporting daily cramps. Only a third of these patients received drug therapy for cramps, most commonly quinine sulfate.

We likewise found that 29% of veterans describe restless legs, with 11% having daily symptoms. Only 28% of symptomatic patients reported drug treatment, most commonly with diazepam.

Finally, we found that 49% of veterans report numbness and tingling in the extremities. Only 21% of those with daily symptoms reported receiving drug treatment, with phenytoin and amitriptyline used equally often.

Conditions especially related to leg symptoms were hypertension, peripheral vascular disease, coronary artery disease, cerebrovascular disease, kidney disease, and hypokalemia. We were surprised that diabetes mellitus was not more closely associated. This lack of association was not due to a lack of study power, as the confidence limits on the odds ratio for diabetes are relatively narrow. Most of our diabetic patients are type II, and this may have accounted for the unexpectedly low rate of dysesthesias. Other factors such as the use of self-reported diagnoses and a lack of confirming data on medications may affect the relationships seen through misclassification and confounding. Further study of the associations found is needed to verify these findings.

In conclusion, we have shown that nocturnal leg cramps, the restless legs syndrome, and numbness and tingling in the legs are common in an outpatient veteran population. Only a third of our population is not bothered by at least one of these symptoms, and a fifth have all three. Yet less than half of

TABLE 5.—*Leg Symptoms According to Self-Reported Diagnoses*

Diagnosis	None: Patients, No.	None: %	1 Symptom: Nocturnal Leg Cramps (NLC)	1 Symptom: Restless Legs Syndrome (RLS)	1 Symptom: Peripheral Neuropathy (PN)	2 Symptoms: NLC & RLS	2 Symptoms: NLC & PN*	2 Symptoms: RLS* PN*	All 3
			Patients, %			Patients, %			Patients, %
Hypertension	151	29	11	0	7	3	18	2	28
Coronary artery disease	108	24	16	1	11	7	13	2	26
Diabetes	105	29	17	0	14	5	10	3	23
Peripheral vascular disease	83	10	10	0	12	4	18	4	43
Low potassium	56	23	13	2	9	9	18	4	23
Stroke	34	15	12	0	24	0	27	3	21
Kidney disease	8	13	0	0	25	0	13	0	50
Low calcium	7	0	0	0	29	14	0	14	43

*Includes dysesthesias.

those with occasional symptoms and only 80% of those with daily symptoms can remember discussing them with their physician. The efficacy of treatment from patient reports is disappointing, even when given. While quinine use effectively relieves nocturnal leg cramps in half the treated patients, none of the regimens used for the restless legs syndrome or the dysesthesias associated with symptomatic peripheral neuropathy were effective. Further research is needed to develop effective treatments for these common and distressing conditions.

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Articles

Animal Rights and Animal Experimentation
Implications for Physicians

ARMAND P. GELPI, MD, *Palo Alto, California*

Practicing physicians are just becoming aware of the animal rights movement, which during the 1980s spawned numerous acts of violence against research facilities throughout the United States. The animal rightists are challenging physicians to show moral justification for the human exploitation of nature and the world of subhuman species. They have aroused public interest in animal welfare, sparked protective legislation for experimental animals, and indirectly encouraged the creation of committees to oversee the conduct of animal experimentation and the conditions of animal confinement. This controversy has necessitated a closer look at the questions of animal experimentation and animal rights against the backdrop of human experimentation and human rights. Physicians and specialists in animal care seek to alleviate suffering and anxiety, and, as moderates, they may be able to bring both sides of the animal rights controversy together in a spirit of mutual tolerance and in the common cause of promoting both human and animal welfare.

(Gelpi AP: Animal rights and animal experimentation—Implications for physicians. West J Med 1991 Sep; 155:260-262)

Physicians have been summoned to the aid of their colleagues, the medical scientists, under siege by the animal rights movement. Recent articles in clinical journals have outlined the history of the antivivisection and animal rights movements in America, and they have highlighted the response of organized medicine—rationalization, philosophical justification, and policy statements—to actual and threatened constraints on animal experimentation.[1,2] Physicians have been exhorted to convince their patients and each other of the merits of animal experimentation and to warn against any restrictions or interruptions.

The animal rights movement until recently had received little attention in clinical journals but considerable coverage by the popular press and in bioscience periodicals. Although there is no clear distinction between medical science and clinical medicine, bioscience researchers have been the primary targets of the rightists. It may therefore surprise clinicians to learn that the animal rights debate now shares center stage with such compelling issues affecting both medicine and society as abortion and the prolife-prochoice controversy, genetic engineering and its human applications, and the rationing of health services. The animal rights movement has aroused frustration and exasperation within the scientific community. Is the future of science in jeopardy? In the interest of animal welfare, will health standards deteriorate? Do animals have rights? If so, are they equivalent to human rights? These questions are difficult to answer if one relies on the tirades from animal rights militants or on the defensive rhetoric from scientists.

Historical precedents for the current animal rights movement were set over a century ago with the antivivisection campaign that arose in England, bringing together an unlikely coalition of feminists, aristocracy (including Queen Victoria), and trade unionists—all protesting against cruelty to animals, degrading examinations and treatment of women at the hands of certain gynecologists, and the deplorable conditions that often existed in hospitals and clinics provided for the poor.[3,4] A popular target for the antivivisectionists was the eminent 19th century physiologist, Claude Bernard, who to them epitomized scientific arrogance and cruelty. When Bernard wrote, "A physiologist . . . no longer hears the cries of animals, no longer sees the blood that flows, he only sees his idea, only the organisms concealing problems which he intends to solve," he guaranteed himself a permanent niche in the rogues' gallery of animal abuse.[5] Yet it was Bernard's single-minded approach to research—his total absorption in its questions and its goals, rather than its process—that should have exonerated him from charges of deliberate cruelty.

The antivivisection movement found its way to the United States, but for a variety of reasons—not the least of which was effective containment by a handful of respected and energetic medical scientists at the turn of the century—it never gained momentum until transformed into the animal rights movement of the late 1970s.[6,7] This delay is reflected in the lack of protective legislation for experimental animals that ended with the passage of the Animal Welfare Act of 1966.[8] Although England had had its Cruelty to Animals Act in effect for the preceding 90 years, the provisions were so ambiguous, evasion so easy, and creative interpretation by researchers so widespread that no scientist has ever been prosecuted.

Australian philosopher Peter Singer revived the antivivisection crusade both here and abroad with his book, *Animal Liberation*, published in the mid-1970s.[9] The idea of animal rights may have caught on at this point precisely because Singer was able to invest the transformed movement for animal protection with some of the sentiments that had aroused the English a century before. His concept of "speciesism"—the exploitation of animals—dovetailed with those of sexism and racism at a time when the nation was examining its collective conscience on these last issues and at a time when the public was entering another cycle of disaffection with science. The scientific community remained largely indifferent to this confluence of grievances until the laboratory

From the Division of Extended Care, Veterans Administration Medical Center, Palo Alto, California.
Reprint requests to Armand P. Gelpi, MD, Division of Extended Care, VA Medical Center, MPD, 116/B5, 3801 Miranda Ave, Palo Alto, CA 94304.

break-ins by radical elements of the animal rights movement in the 1980s.[10]

The movement has picked up speed and adherents despite attempts by some scientists to discredit the animal protection bloc, portraying it as a mix of dotty old women, affluent busybodies, sentimental fools, and terrorists. It is unfortunate that in the case of the more militant organizations, such as People for the Ethical Treatment of Animals, criminal acts of extremists have damaged the reputations of all advocates and obscured their message. It is no less regrettable that, with the possible exception of the Humane Society of the United States, the moderate leadership within the animal welfare organizations has neither disassociated itself from its radical elements nor condemned the trashing of research facilities and the thefts of experimental animals. Like other radicals from earlier years, those representing the animal rights movement see justifying precedents for breaking the law in historical images of social reform—avenues of progress littered with the bones of sacrificial reactionaries and the shards of outdated institutions.

In the final analysis, the animal rights movement goes far beyond the issue of animal experimentation. It is concerned with the plight of those millions of animals slaughtered to satisfy our inflated appetites for meat, the millions destroyed in the course of product safety testing, the millions brutally killed for their pelts and furs, the millions sacrificed for trophies in the name of "sport," the millions of lost or abandoned pets put down in animal shelters, and the relentless extermination of endangered species. The rightists see this parade of misery, death, and environmental depredation as a type of genocide—a monstrous crime against nature.

The animal rightists ask a fundamental question: "By what right do you scientists justify animal experimentation?" The usual response begs the question with "for human salvation" or "for the advancement of science." Aside from wrestling with troublesome moral questions, most researchers see little hope of giving up animal experimentation because it is an essential, if less often used, tool for bioscientific inquiry. When not philosophizing, the rightists complain that much animal experimentation is an unnecessary duplication of previous research. They assert that the health of the nation is a by-product of economic growth—sanitation, improved nutrition, and better housing—rather than a direct result of animal experimentation. They question the assumption that noble motives underlie research on animals, and even scientists balk at the suggestion that at the heart of every animal experiment is the hope or expectation that somehow the work will lead to the relief of human suffering or the prolongation of human life.

Until the laboratory break-ins of the past decade, with their disclosures of inferior standards of animal care in some of the vandalized facilities, and until the enactment of additional federal legislation in the form of amendments to the 1966 welfare act that provided more exacting standards of animal care and experimentation, some scientists viewed the animal rightists with scorn or amused detachment. Others only grudgingly conceded that there had ever been a need for the protection of experimental animals or that this protection should be ensured by legislative safeguards and by the creation of animal welfare committees for research facilities. They denied that laws had been broken or that abuses apparently uncovered by rightist raiders were in fact abuses. This holding pattern has given way to alarm, to initiatives for educating the public on the merits of unrestricted animal experimentation, and to the characterization of animal rights apologists as enemies of science.[11-13] The label seems unfair, if only because animal experimentation has a limited role in biomedical research and because biosciences represent but a fraction of science. Moreover, most of us were taught that science consists of a rigorous type of inquiry to test certain hypotheses in search of the truth, rather than simply an array of embattled researchers with their expensive equipment and captive animals. Better to charge the animal rights moderates with philosophical error and the militants with vandalism and robbery.

On one point both sides would agree: most, if not all animal experiments would be unthinkable with human subjects. Or would they? On the eve of World War II, ignoring the record of adverse behavioral changes in primates subjected to prefrontal lobotomy[14] and lacking an animal model for human psychosis, a prominent American neurologist and a collaborating neurosurgeon nevertheless set out to cure psychosis by coronal section of the anterior forebrain in mentally ill patients.[15] Their technique might be charitably described, even for the times, as primitive and blind. There was no public outcry, and there was virtually no peer criticism other than restrained debate in professional journals.[16] Later, many psychiatrists would be doing this procedure, which during its heyday, from 1949 to 1952, was carried out on several thousand mentally ill patients a year.[17] Sad to say, this operation was never convincingly shown to have been of benefit, and it was not until 1973 that statutes were in place to regulate this and other types of psychosurgery.[18] Many scientists and most of those representing the animal welfare bloc would regard this type of experimentation as a fair illustration of the blurred boundary between human and animal rights abuse.

Despite increasing constraints on animal experimentation in our time, the pace of discovery in medicine and other biosciences will increase, with or without a public sensitive to the animal rights issues, with or without added legislative controls on animal experimentation, and despite animal welfare committees. Both sides of the animal rights controversy must agree on some basic premises before they can come together in a common cause that sets reasonable standards for animal welfare, while allowing for humane and essential experiments on animals.[19] The future lies with the moderates in both camps, and there are some encouraging signs. Veterinarians, representing animal care facilities at major universities, are speaking out for increasing sensitivity to the physical and social needs of captive animals and for further refinements in experimental techniques and anesthesia to protect animal subjects from pain and anxiety.[20] There is a final irony to the animal welfare issue that is completely ignored by the rightists and often forgotten by researchers: a substantial proportion of animal experimentation is concerned with restoring health and alleviating suffering in both domestic and wild animals.

Physicians may well have a key role in resolving some of the differences between the animal welfare coalition and scientists. This role should be neither to simply echo the charges of offended scientists nor to necessarily preserve the status quo with animal experimentation. Physicians whose commitments to direct patient care often remove them from contact with the laboratory and participation in research could gain valuable insights about current standards for the humane

treatment of experimental animals from visits to animal care facilities and familiarity, even participation, with animal care committees in place at medical schools throughout this country. For those physicians wishing to view the issue of animal welfare from the rightists' perspective, selections from such publications as *The Animals' Voice, The Animals' Agenda*—published by the Compassion for Animals Foundation, Inc and the Animal Rights Network, respectively—and *The Bulletin of the National Antivivisection Society* may be helpful. Finally, physicians, aside from their early training in the scientific method and their exposure to the life sciences, are by nature and tradition caring persons. They are the chief representatives of the caring professions. In this capacity they may be the most effective arbiters for both sides of the animal rights controversy.

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Articles

Durable Power of Attorney for Health Care
Are We Ready for It?

MARY KANE GOLDSTEIN, MD; ROBERT P. VALLONE, PhD; DENNIS C. PASCOE, MSW; *and* CAROL HUTNER WINOGRAD, MD, *Palo Alto, California*

Health care professionals need to be well informed about advance directives for medical care in the event a patient becomes incapacitated. The Patient Self-Determination Act requires that all patients be advised of their options at the time of hospital admission. Hospitals and health care professionals will need to work together to plan for implementing this law.

We surveyed 215 physicians, nurses, and social workers at a Veterans Affairs Medical Center about the California advance directive, the Durable Power of Attorney for Health Care. Attitudes were generally positive. All of the social workers had heard of the durable power of attorney directive, but 36% of physicians and nurses had never heard of it and an additional 20% had no experience with one. For respondents who had heard of the directive, the mean knowledge score was 6.35 of a possible 10 (5 predicted by chance). Respondents brought up the issue of durable power of attorney with patients before a crisis only 19% of the time and determined whether one had been signed for only 16% of older patients in hospital. The most commonly cited reasons for failure to discuss this with patients were lack of proper forms, pamphlets, or a place to refer a patient. Of those who had ever seen such a document in use, 42% were aware of a problem with it at some time.

Whereas attitudes toward advance directives are positive, many physicians and nurses had little knowledge of the Durable Power of Attorney for Health Care and were poorly equipped to discuss it with patients. We encourage educating hospital staff to prepare for the enactment of the Patient Self-Determination Act. We also recommend that the concerns raised by professionals about the use of a durable power of attorney be addressed.

(Goldstein MK, Vallone RP, Pascoe DC, Winograd CH: Durable power of attorney for health care—Are we ready for it? West J Med 1991 Sep; 155:263-268)

The Patient Self-Determination Act,[1] passed by the United States Congress in 1990 and scheduled to take effect in December 1991, requires hospitals, nursing homes, hospices, and some other agencies that participate in Medicare or Medicaid to inform patients of their rights under state law regarding advance directives and to note in a patient's medical record any directives given by the patient (L. Sloane, "'91 Law Says Failing Patients Must Be Told of Their Options," *New York Times*, December 8, 1990, p 18).[1] Health care professionals in hospitals will help implement this legislation by answering patients' questions about advance directives. As hospitals develop plans for implementation, they will need to address the questions of whether professionals' attitudes are favorable toward the use of advance directives and whether professionals are familiar with the advance directives available in their state.

Legislation enacted by the state of California in 1984, known as the Durable Power of Attorney for Health Care (DPAHC), is a prototype of advance directives now used in many states.[2-4] It allows a competent adult to designate a person—a proxy decision maker—who will have the authority to give or withhold informed consent for medical procedures should the designator lose mental competence. The use of a durable power of attorney has been widely promoted by senior citizens groups and medical associations, as well as in the medical literature[5-9]; some Alzheimer's centers and nursing homes recommend it routinely.[10,11] The high rate of dementia in the elderly[12] and the right of a state to require "clear and convincing evidence" of a patient's wishes[13] argue for written advance directives. While a number of studies are emerging of patients' experience with DPAHC,[14-16] there is little information about that of health professionals. Health care professionals are key to the use of advance directives because they counsel patients. One study showed that physicians have positive attitudes toward advance directives, yet nothing is known about the attitudes of social workers and nurses, nor about knowledge levels of any of these groups.[17] The goal of our study was to describe health care professionals' attitudes, knowledge, and encouragement for the use of California's DPAHC by patients, their reasons for not encouraging use, and problems they encountered with its use. Professionals from different disciplines may vary in their attitudes, knowledge, and levels of support for using the DPAHC and in their reasons for not using it. Accordingly, we compared social workers, nurses, and physicians.

Methods

Questionnaire Design

A questionnaire was developed with the following subsections:

- Demographic data included age, sex, date of gradua-

From the Division of Endocrinology, Gerontology, and Metabolism, Stanford University Medical Center, Stanford (Drs Goldstein and Winograd), and the Geriatric Research, Education, and Clinical Center, Veterans Administration Medical Center, Palo Alto (all authors), California.

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Reprint requests to Mary K. Goldstein, MD, Geriatric Research, Education, and Clinical Center (182B), VA Medical Center, 3801 Miranda Ave, Palo Alto, CA 94304.

1. To execute a valid Durable Power of Attorney for Health Care, is it necessary to consult a lawyer? [No]
2. To execute a valid Durable Power of Attorney for Health Care, is it necessary to consult a physician? [No]
3. To execute a valid Durable Power of Attorney for Health Care, is it necessary to consult the next of kin? [No]
4. What happens if someone names his or her spouse as decision maker and later they get divorced? Is the Durable Power of Attorney document automatically nullified? [Yes]
5. Someone executes a Durable Power of Attorney and files it away with his or her will. Ten years later that person becomes incapacitated and the Durable Power of Attorney document is found. Is it still valid? [No]
6. Are physicians legally bound to recognize the right of the person appointed in the Durable Power of Attorney to give or withhold consent for medical treatment unless the appointment is overturned in court? [Yes]
7. Are physicians legally bound to follow the instructions in a living will? [No]
8. Does the Durable Power of Attorney take effect only if the patient is terminally ill? [No]
9. May a close friend be appointed as the agent or decision maker under the Durable Power of Attorney for Health Care? [Yes]
10. May the family physician be appointed as the agent or decision maker under the Durable Power of Attorney for Health Care? [Yes]

Figure 1.—Ten questions were developed to measure health care professionals' knowledge of the Durable Power of Attorney for Health Care (DPAHC). Questions 1 through 3 are basic to the idea that the DPAHC enhances individual autonomy and ability to act without consulting usual authorities. Questions 4, 5, and 10 address safeguards against misuse built into the legislation. Questions 6 and 7 differentiate the DPAHC from a living will. Question 9 addresses the right to name a nonrelative, important for those without close kin and for persons in close but nonmarital relationships, such as gay couples.

tion from professional school, number of patients in hospital per month, and percentage of patients who are elderly.

- Attitudes were measured by three questions on a nine-point scale. The first dealt with attitudes toward patient autonomy, the second the importance of advance planning for decisional incapacity, and the third the importance of the proxy form of advance planning. The attitude questions were written in a way that allowed even those who had never heard of the DPAHC to give a response.

We then asked respondents whether they had heard of the DPAHC before receiving the questionnaire. Those who replied "yes" are reported as having previous awareness of it. All subsequent questions depended on having heard of the DPAHC and were asked only of this group.

- Professionals' activities supporting the use of DPAHC by patients were assessed. First, the professionals were asked how often they bring up the issue of DPAHC with older patients before a crisis arises. Second, they were asked to specify the number of patients admissions of older persons they had been involved with in the past month. They were then asked to specify for how many of these patients they had determined whether a DPAHC had been signed. These two questions thus gave a percentage of admissions for whom the provider had sought the presence of a durable power of attorney.
- In addition to a previous awareness of DPAHC, a knowledge of DPAHC was measured by ten questions selected to emphasize knowledge of the safeguards of patients' rights and to distinguish the DPAHC from the living will (Figure 1). Questions included who must be consulted, what happens in the event of a divorce, time limitation, physicians' responsibility, and who may be appointed. The questions were reviewed for accuracy by Myra Gilfix, JD, Palo Alto, California, an attorney specializing in elder law who has written extensively on the subject of the DPAHC.
- Seven reasons for a lack of support for the Durable Power of Attorney for Health Care were presented, and respondents were asked to indicate which had ever contributed to their failure to bring it up with patients.
- Respondents were asked how recently they had seen a DPAHC in use and to identify problems encountered with its use.

The project received approval from the Stanford University Medical Center Human Subjects Committee. The questionnaire was pilot tested in two phases. Geriatricians familiar with the DPAHC reviewed the questionnaire for content. Fifteen representatives of the disciplines to be sampled, chosen from area academic hospitals not included in the study, then completed the questionnaire and an attached survey on readability, time for completion, and appropriateness to professional practice. The questionnaire was administered in the summer and fall of 1988.

Subject Selection

Health care professionals at Stanford University Hospital and the affiliated Palo Alto Veterans Affairs Medical Center were sampled as follows:

Social workers. All social workers (34) were surveyed; responses were received from 31 (91%).

Nurses. A list of nurses was obtained, and nurses with strictly administrative positions were excluded, as were nurses on pediatric and obstetric units. The remaining 1,125 were numbered consecutively, and a sample of 40 was selected by random number. Responses were received from 35 (90%).

Physicians. A list was obtained of all physicians on staff.

TABLE 1.—*Demographic Profile of Respondents*

Demographics	Profession: Social Worker n=31	Nurse n=35	Physician n=150	All n=216
Response rate, %	91	87	63	...
Experience, median yrs.	13	7	11	...
Male sex, %	29	6	87	...
Patients admitted to hospital/respondent/mo, median No.	45	52	26	35
Respondents' patients older than 65, % (SD)	46.5 (26)	58.8 (25)	44.0 (19)	46.7 (22)

SD = standard deviation

TABLE 2.—*Interdisciplinary Comparison of Attitudes*

Attitude*	Profession: Social Worker n=31	Nurse n=35	Physician n=148	All† n=214
	mean (standard deviation)			
Patient autonomy (9=greatest autonomy)	6.29 (1.6)	6.30 (1.7)	5.8 (1.6)	5.96 (1.6)
Importance of patient-doctor discussions of advance medical decision making (9=not important, 0=essential)	1.71 (0.6)	1.94 (0.8)	2.12 (1.1)	2.05 (1.0)
Importance of proxy appointment (9=very unimportant, 0=very important)‡	2.03 (1.4)	2.19 (1.0)	2.32 (1.2)	2.26 (1.2)

*Attitude was determined using a 0 to 9 scale.
†None of these differences between disciplines were significant as measured by analysis of variance.
‡Such as the Durable Power of Attorney for Health Care.

TABLE 3.—*Provider Activities to Encourage the Use of the Durable Power of Attorney for Health Care (DPAHC) by Patients*

Provider Activity	Profession: Social Worker n=29	Nurse n=28	Physician n=99	All n=156
Provider's estimate of % time he/she introduces topic				
Percent	28	12	19	19
Range	0-80	0-100	0-90	0-100
Median	15	0	9	9
SD	25	23	24	24
Admissions for which provider sought DPAHC, %	24	14	14	16

Specialists with little contact with elderly patients (pediatricians and obstetricians) or with little primary care responsibility (anesthesiologists, dermatologists, pathologists, and radiologists) were excluded. The remaining 837 physicians were then stratified to avoid overrepresenting some subgroups. Physicians were classified as nonsurgical or surgical, as community office based or as hospital based, and house staff or attending level. A random sample of 40 was then taken from each of the six categories thus formed: community-based surgical attending, community-based nonsurgical attending, hospital-based surgical attending, hospital-based nonsurgical attending, surgical resident, nonsurgical resident. Questionnaires were coded for confidentiality. Responses were received from 150 (63%).

Data Analysis

Data were checked for accuracy by comparisons with known data for the subject, such as specialty, approximate age, and sex, and by a cross-check of unusual responses to the number of patients seen. An overall index of knowledge was computed by adding the number of correct answers on the knowledge questions. Frequencies, *t* tests, χ^2 analyses, and analyses of variance were computed with SPSS-PC [Statistical Package for the Social Sciences-Personal Computer] statistical software. Criteria were met that ensure that analysis of variance and χ^2 remain valid with unequal sample sizes.*

Results

The demographic data on the respondents show that we reached a sample with a wide range of experience, including some with extensive experience with the elderly (Table 1). In general, respondents had favorable attitudes toward patients' autonomy and the use of advance directives (Table 2). There were no significant differences in attitude among physicians, nurses, and social workers.

*Professor Lincoln Moses provided statistical advice.

Table 3 shows the mean response to how often respondents introduce the topic of the DPAHC with older patients before a crisis and for what percentage of admissions of older persons in the previous month the respondent had sought the presence of a DPAHC. By self-report, professionals do not often introduce the topic of a DPAHC before a crisis.

Of those surveyed, 151 (70%) responded "yes" rather than "uncertain" or "no" that they had heard of the DPAHC before receiving the questionnaire: social workers, 100%; nurses, 67%; physicians, 64% (χ^2 15.9, $P = .0004$).

Of all respondents who had previous awareness of the DPAHC or who were uncertain whether they did, 161 completed the knowledge questions. The mean scores (10 = perfect score) by discipline are shown in Table 4.

The response to the offered reasons for lack of support for the DPAHC are listed in Table 5. Handwritten comments included ones from seven physicians who thought that another person should discuss DPAHC: Four respondents thought it inappropriate to discuss the DPAHC with a healthy patient, and three physicians said that physicians should not be involved in discussions of a DPAHC. One respondent wrote, "Surgeons who address this issue with often healthy middle-aged patients do not instill confidence . . . ." In contrast, another surgeon wrote that the DPAHC discussions should be mandatory before high-risk surgical procedures are done.

Table 6 shows how recently respondents had observed the use of a DPAHC in any way. Many had never seen one used. Of the 113 respondents who had ever seen a DPAHC in use, 47 (42%) had been aware at some time of a problem with its use. When asked to identify the problem, 17 (15%) reported that a patient was not competent at the time a DPAHC was executed; 8 (7%) reported coercion in the choice of a proxy; 16 (14%) reported that the form was too complicated to understand; and 23 (20%) reported that the person named was incompetent, unavailable, or inappropriate.

TABLE 4.—*Knowledge of the Durable Power of Attorney for Health Care (DPAHC)**

Score	Profession: Social Worker n=31	Nurse n=29	Physician n=101	All n=161
Mean knowledge score (SD)†	7.15 (1.58)	5.50 (1.85)	6.35 (1.91)	6.35 (1.90)

*Knowledge was surveyed by 10 questions with yes or no answers; perfect score = 10. Knowledge questions were asked only of subjects who had previously heard of DPAHC.
†F = 5.97, P = .003.

TABLE 5.—*Reasons for Not Initiating Discussion of the Durable Power of Attorney for Health Care (DPAHC) With Patients**

Reason	Profession: Social Worker n=31 %	Nurse n=26 %	Physician n=96 %	All n=153 %
Don't have proper pamphlets or forms	30	79	52	53†
Don't know how to get the person started, where to refer	17	48	37	35
It was inappropriate for provider to bring up	27	31	25	26
Too time-consuming	20	28	27	26
Patient will feel offended	23	41	16	22
Professional thinks that someone else routinely discusses it	10	17	12	12
Most patients can't understand it	14	5	7	10

*A checklist of possible reasons for not initiating a discussion of DPAHC was offered to subjects who had heard of it. Responses shown are the percentage who endorsed each offered option. More than 1 answer was allowed.
†χ^2 = 16.01, P = .003.

Physician subgroups did not significantly differ in attitudes or on knowledge scores.

Discussion

Response bias is a concern in survey research. We attempted to eliminate bias in several ways. We chose a questionnaire rather than an interview format to allow for less socially desirable responses on this sensitive topic.[18-20] The range of responses, including both low and high support for DPAHC, suggests that we achieved a representative sample.

Our survey was conducted at a time when the California Durable Power of Attorney for Health Care was under intense discussion at Stanford University Hospital and the Palo Alto Veterans Affairs Medical Center. The DPAHC act had been in place for about four years. The hospital was considering whether to include information about it in the standard patient admission packet, several departments had held business meeting discussions or grand rounds on the topic, and the medical center's ethics committee had published an article in *The New England Journal of Medicine* in which the DPAHC was discussed.[21] The veterans hospital had a policy on how to direct patients' questions about the DPAHC and how to record documents on patients' charts. Both institutions had a small cadre of persons who were familiar with the DPAHC, and the institutions were poised to begin disseminating information about it. In that sense, the situation was analogous to what will be expected in 1991 at many institutions nationwide when they begin to plan programs to implement the Patient Self-Determination Act. Recent publicity about the Cruzan case makes it likely that more professionals will have heard of advance directives, but just as in our sample, even those who have heard of the advance directive may have little understanding of the details of it. The findings of this study may help in planning educational programs.

The most important finding of our study is that health care professionals are ill prepared to inform patients about advance directives. Others have documented patient wishes to discuss life-sustaining treatment and the infrequency of such discussions.[22-24] A family care giver has written movingly on advance planning (A. H. Malcolm, "The Ultimate Decision," *New York Times Magazine*, December 3, 1989, p 38). A recent court decision underscores the importance of written, rather than oral, directives ("Conflicting Decisions of Tube Feeding: NY High Court and RI Federal Court," Society for the Right to Die *Newsletter*, winter 1988, pp 1, 4). In this context, well-informed health care professionals are imperative.

TABLE 6.—*Provider Observations of Use of the Durable Power of Attorney for Health Care (DPAHC) by Patients**

Observation of Use	Profession: Social Worker n=31, No. (%)	Nurse n=26, No. (%)	Physician n=96, No. (%)	All n=153, No. (%)
Never	5(16)	12(46)	24(25)	41(27)
Within past week	8(26)	1(4)	14(15)	23(15)
Within past month	7(23)	5(19)	23(24)	35(23)
More than 1 month ago	11(36)	8(31)	35(36)	54(35)

*For subjects who had heard of the DPAHC, the timing of when they had last seen DPAHC in use in any way is analyzed. The percentage is of those who had heard of the DPAHC.

When asked about reasons for not initiating discussions of the Durable Power of Attorney for Health Care, respondents most frequently cited a lack of the proper pamphlets or forms and a lack of knowledge of where to refer patients. Professionals are reluctant to initiate discussions about a topic they feel ill equipped to pursue in detail.

A tension exists in medical ethics between the principle of beneficence and that of patient autonomy, with the current balance toward patient autonomy.[25-31] A serious attempt has been made to extend the rights of patient autonomy to the "formerly competent" by means of advance directives.[4,6,32-37] Patients will not, however, be able to benefit from advance directives if the health care professionals who are entrusted with carrying them out do not understand and support them. If professionals do not look for the advance directive until a need arises, they will likely find a patient mentally incapacitated and unable to tell them whether one exists. Cognitive impairment in elderly patients in hospital for acute medical problems is common and often unrecognized[38]; complex decisions such as proxy appointment should be made, when possible, in advance of an emergency.

Social workers were much more likely to have heard of the Durable Power of Attorney for Health Care and had significantly higher knowledge scores than physicians and nurses. Social workers and nurses placed greater emphasis on patient autonomy than did physicians: It has been suggested that physicians are less willing than nurses to share their position of power.[39] Social workers were the most likely to encourage the use of a DPAHC by patients. This is in keeping with traditional role definitions that give social workers responsibility for future planning with patients about financial and legal matters. Nurses had previous awareness of DPAHC as often as physicians but were the least likely to bring it up for discussion. It is possible that many nurses do not bring it up for discussion because they feel it is the primary physician's role to do so.

Advance directives provide a powerful extension of rights for patients who are sophisticated enough to anticipate their own wishes in a variety of hypothetical medical situations, who have a trusted friend or relative willing to shoulder the responsibility, and who have several alternatives in case the trusted friend or relative becomes incapacitated first. They are not, however, a panacea for the dilemma of an incompetent patient who requires medical attention (M.K. Goldstein, "Power of Attorney (Letter)," *New York Times*, December 23, 1990, p 10). Studies have found discrepancies between decisions by the patient and the potential proxy, a lack of applicability of one clinical situation to another, discrepancies between patients' and physicians' perceptions of quality of life, an unwillingness of the general public to make life-support-withdrawal decisions for a relative, and changes in patients' preferences over time.[40-45] The problem of sham proxy appointment for an already incompetent patient has also been reported.[46]

We found that almost half of the professionals who had ever seen a Durable Power of Attorney for Health Care in use claimed to have been aware of a problem with it, such as the appointed proxy being incompetent also. The report of patients not competent at the time a DPAHC was executed suggests the need for further education about competency assessment.[47-50] The standard for legal capacity to execute a DPAHC is analogous to that for testamentary capacity, which allows for a noticeable degree of mental impairment provided the patient has task-specific competence.[51,52]

Conclusion

Most health care professionals in this survey were unprepared to discuss the Durable Power of Attorney for Health Care with patients. We recommend educational programs that provide basic information and also address the specific problems encountered in past use, and we encourage discussion before an emergency arises so that patients will have an opportunity to think it over and discuss it with family members. Future research should explore the extent to which professionals follow instructions provided in an advance directive, patient and family satisfaction with its use, and the effects of the implementation of the Patient Self-Determination Act. Future research might also explore the health cost consequences of the use or nonuse of an advance directive, but such research must safeguard against coercing patients to sign a document that will limit treatment in the interests of reducing costs.

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Articles

Public Perceptions of Health Care Problems
An Analysis From Arizona

BRADFORD L. KIRKMAN-LIFF, DrPH, *Tempe, Arizona*

Public perception of 17 health problems was assessed by telephone and in-person interviews in Arizona. Drug abuse (64.7%), the costs of health care (62.8%), and drunk driving (60.6%) were considered the most serious health care problems. Elderly and rural residents tended to view drug abuse, drunk driving, teenage pregnancy, and economic aspects of health care as less serious than did the younger and urban respondents, while the poor thought these problems were more serious. Respondents in this survey were less concerned with the lack of specific clinical services for high-risk groups—the old and frail, pregnant women, people with the acquired immunodeficiency syndrome, suicidal teenagers, and abused children.

(Kirkman-Liff BL: Public perceptions of health care problems—An analysis from Arizona. West J Med 1991 Sep; 155:269-273)

At a time of increasing national debate over the merits of alternative forms of universal health care coverage or national health insurance, coupled with calls from industry and labor for effective cost-containment strategies, it is essential for physicians and other health care policymakers to have accurate assessments of the opinions of the general public on a variety of health issues. Rochefort and Boyer stated that polls can assist in "identification of priorities among competing social values, analysis of the social environment in which public programs must operate, and evaluation of programmatic impacts."[1] I present the results of one statewide effort to assess the public's perception of various health problems.

Methods

The data for this analysis were collected by Louis Harris and Associates, Inc, as part of a larger statewide survey on health care in Arizona. These data are drawn from a three-stage sample of 3,104 adults surveyed by telephone and in-person interviews. Of the total adult interviews, 3,004 were conducted by telephone from the Harris firm's headquarters in New York from February through May 1989. These telephone interviews were conducted in two stages. In stage one, interviews were conducted with a representative cross section of 2,000 adults contacted through random digit dialing followed by random selection of one adult in each household, using Troldahl-Carter-Bryant grids. In stage two, additional telephone interviews were conducted with 1,004 adults at or below the poverty level. This oversample of low-income persons was obtained by screening additional households drawn from the same bank of telephone numbers in which low-income persons had been found in the cross section. A household was screened out if its income exceeded the poverty level. There was an overall refusal rate of 22% and an interview termination rate of 6%. In both stages of the telephone interviews, rural areas were oversampled to provide more extensive information about less populated areas, while Maricopa County, with more than half the population of the state, was undersampled. Finally, 100 in-person adult interviews were conducted in households without telephones. These in-person interviews were done in selected census tracts in Phoenix, Tucson, and Yuma that had the lowest proportion of households with telephones and the highest proportion of households below the federal poverty line. All telephone and in-person interviews were conducted in English or Spanish. The oversampling of poor and rural households and the in-person interviews were corrected by weighting.[2]

Surveyors asked all adults for their view of the extent to which each of 17 health issues was a problem in their community. The specific question was, "Would you say that X is a major problem, a minor problem, or not a problem in your community?" The 17 problems were selected from a longer list after advice from members of the Arizona Medical Association and six other health-related organizations. The final items represented those issues for which there were active efforts at state legislative action in Arizona. They represent a list of politically sensitive health issues and exclude issues such as cigarette smoking, which at the time of the survey was not receiving political attention. The order in which these issues were presented to each respondent was varied randomly to avoid possible bias by asking the issues in a fixed order.

Surveyors also collected information on six demographic variables. There were two residence categories: urban (Maricopa and Pima Counties, which include Phoenix and Tucson, respectively) and rural (the rest of the state). Household income was categorized as poor (below the federal poverty line, which is based on actual household income and family size), near-poor (between the federal poverty line and 185% of the federal poverty line), and nonpoor (over 185% of the federal poverty line). There were three education categories: less than high school, high school, and more than high school, and four ethnicity categories: anglo, Latino, African American and Native American, using the suggestions of Hayes-Bautista and Chapa.[3] Age was grouped into three cate-

From the School of Health Administration and Policy, College of Business, Arizona State University, Tempe.

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Reprint requests to Bradford L. Kirkman-Liff, DrPH, Associate Professor, School of Health Administration and Policy, Arizona State University, Tempe, AZ 85287-4506.

TABLE 1.—*Perception and Ranking of Health Care Problems in Arizona, 1989*

Health Care Problem	Rank	Perception, %			
		Major Problem	Minor Problem	Not a Problem	Not Sure
Drug abuse	1	64.7	24.1	7.1	3.9
Cost of health care	2	62.8	19.7	11.7	5.8
Drunk driving	3	60.6	26.1	8.5	4.7
People with no health insurance	4	54.8	21.8	10.9	12.4
Teenaged pregnancy	5	53.5	26.5	10.5	9.5
Cost of medical malpractice insurance	6	52.3	16.7	13.7	17.2
Child abuse	7	45.3	29.2	16.6	8.8
Lack of services for the mentally ill	8	42.4	25.8	16.7	15.0
Lack of services for the old and frail	9	37.9	28.3	22.9	10.7
Pregnant women not getting prenatal medical care	10	32.9	29.8	20.7	16.3
People who have AIDS	11	30.9	32.0	23.2	14.0
Teen suicide	12	29.9	34.1	24.2	11.6
People not knowing where to go for the services they need	13	27.1	39.5	26.1	7.2
Lack of transportation to get to doctors and hospitals	14	23.3	34.2	36.0	6.5
Lack of dental services for children	15	18.9	25.5	39.6	15.9
Infant mortality	16	16.0	33.4	29.4	21.1
Emergency and ambulance service	17	13.3	27.9	50.6	8.2

AIDS = acquired immunodeficiency syndrome

TABLE 2.—*Perception and Ranking of Selected Health Care Issues, by Age*

Health Care Problem	Age of Respondent						χ^2
	17 to 39 years		40 to 64 years		≥ 65 years		
	Rank	%	Rank	%	Rank	%	P<.001
Drug abuse	1	63.3	2	69.8	2	51.3	131.0
Cost of health care	2	60.0	1	73.4	3	50.9	66.2
Drunk driving	3	59.5	3	66.9	1	52.6	63.8
People with no health insurance	4	56.8	5	62.2	6	34.5	78.1
Teenaged pregnancy	5	55.8	6	55.9	5	42.5	115.5
Cost of medical malpractice insurance	6	46.8	4	64.7	4	46.4	78.6
Child abuse	6	46.8	8	48.5	6	34.5	111.5
Pregnant women not getting prenatal medical care	8	36.6	11	33.5	13	20.3	85.5

gories: 17 through 39, 40 through 64, and 65 and older. The employment status of the household's main wage earner was categorized as employed (either full-time or part-time), unemployed, and not in the labor force (retired, full-time student, full-time homemaker).

The analysis of these questions took several directions. The overall distribution of responses allows a rank order to be assigned to each of these 17 problems. Cross-tabulations of each item with each demographic measure were used to test for significant differences among demographic subgroups as to the perceived seriousness of these problems. These analyses were also used to develop a rank ordering of the problems for each subgroup within the state.

Results

Table 1 presents the overall public perception of the 17 health problems in Arizona. Nearly two thirds of the surveyed adults in Arizona (64.7%) thought that drug abuse was a serious problem in their community, and only 7% thought that it was not a problem. Close behind were the cost of health care, which was seen as a major problem by 62.8% of those surveyed, and drunk driving, which was considered a major problem by 60.6%. Some 11.7% of the respondents thought that the costs of health care were not a problem, while only 8.5% of the general public thought that drunk driving was not. I used the percentage who thought that an issue was a major problem as the basis for rank ordering, and so the cost of health care has been ranked as the second most important problem and drunk driving as the third most important.

These findings should be interpreted with caution. For example, the relatively high percentage of adults who think that teenaged suicide is not a problem in their community (24.2%) may be due to a lack of awareness of the number of cases of teenaged suicide. The small percent who thought that infant mortality was a major problem may not have understood the issue, as indicated by the 21.1% who were not sure on that question.

The same analysis was conducted for various demographic subgroups of adults, by doing cross-tabulations of each of the 17 problems with each of the six demographic measures. The χ^2 tests for each of these 102 analyses were used to identify significant differences among demographic subgroups as to the perceived seriousness of these problems. These analyses were also used to develop a rank ordering of the problems for each subgroup within the state.

Age

When the results are examined for the three age groups (Table 2), the 65-and-older group tends to view all health problems as being less serious than do the younger age groups. Some 52.6% of the elderly ranked drunk driving as a major health problem, the highest ranking of the 17 problems. In contrast, 66.9% of the 40-through-64-year-old

group and 59.5% of the 17-through-39-year-old group thought that drunk driving was a major problem. The younger groups gave drunk driving a higher rating, yet this problem was only the third most important among these groups, with drug abuse and the cost of health care having even higher ratings and rankings.

The oldest group surveyed gave two issues much lower rankings and lower ratings than did the other groups. First, the number of people with no health insurance was seen as a major problem by only 34.5% of the 65-and-older group, as opposed to 56.8% of the 17-through-39-year-old group and 62.2% of the 40-through-64-year-old group. Second, the number of pregnant women not receiving prenatal care was seen as a major problem by only 20.3% of the 65-and-older group, as opposed to 36.6% of the 17-through-39-year-old and 33.5% of the 40-through-64-year-old group. Much smaller percentages of the 65-and-older group rated teenage pregnancy a serious problem than did other groups.

Education

There are only a few differences in problem ranking when the education of the respondents is considered (Table 3). The cost of malpractice insurance was the second most serious problem for those with more than a high school education: it was rated a major problem by 64.4% of the population in this category. The issue is perceived differently by the other groups. Slightly more than half (50.7%) of respondents with a high school education thought that the cost of malpractice insurance was a serious problem. Relative to the other issues, that subgroup ranked it sixth in importance. Only 38.1% of those with less than a high school education thought that it was a major problem, which gave it a rank of 9.

Those with less than a high school education considered the lack of services for the frail and elderly, people with the acquired immunodeficiency syndrome (AIDS), and people not knowing where to go for services to be more important than did the other groups. Those with more than a high

TABLE 3.—*Perceptian and Ranking af Health Care Prablems, by Educatian Level*

	Educatian af Respondent						
	Less Than High School		High School		More Thon High Schaal		χ^2
Health Care Problem	Rank	%	Rank	%	Rank	%	P<.001
Cost of medical malpractice insurance	9	38.1	6	50.7	2	64.4	60.7
Lack of services for the old and frail	7	44.1	9	35.2	10	36.4	25.1
Pregnant women not getting prenatal medical care	13	31.2	10	29.1	9	38.3	24.7
People who have AIDS	10	37.7	11	27.2	12	30.0	71.0
People not knowing where to go for the services they need	11	36.5	12	25.6	14	22.2	66.4

AIDS = acquired immunodeficiency syndrome

TABLE 4.—*Perception and Ranking of Health Care Problems, by Emplayment af Main Wage Earner*

	Emplayment of Main Wage Eorner						
	Employed		Unemployed		Not in the Labor Force		χ^2
Health Care Problem	Rank	%	Rank	%	Rank	%	P<.001
Teenaged pregnancy	5	54.6	2	64.9	5	47.4	53.0
Cost of medical malpractice insurance	6	54.3	12	34.4	4	48.7	15.6*
People who have AIDS	12	30.7	7	47.4	10	27.5	46.9
Teen suicide	11	31.3	10	39.1	13	24.7	59.6

AIDS = acquired immunodeficiency syndrome

*P = .004

TABLE 5.—*Perceptian and Ranking af Health Care Prablems, by Ethnicity*

	Ethnicity of Respondent								
	Anglo		Latino		African American		Native American		χ^2
Health Care Problem	Rank	%	Rank	%	Rank	%	Rank	%	P<.001
Drug abuse	2	60.4	1	72.5	1	66.7	2	77.9	31.6
Cost of health care	1	63.1	4	60.8	3	61.6	3	70.0	4.7*
Drunk driving	3	59.5	5	60.4	4	61.4	1	78.7	22.5
People with no health insurance	5	52.9	3	61.5	2	62.4	4	58.9	23.9
Teenaged pregnancy	6	50.1	2	65.4	5	60.5	3	70.0	61.5
Cost of medical malpractice insurance	4	56.6	10	36.7	12	35.2	7	42.8	60.2
Child abuse	7	44.0	6	51.9	8	39.1	6	44.7	26.3
Lack of services for the old and frail	9	36.4	7	44.5	7	53.0	13	24.3	31.8
People who have AIDS	12	28.0	8	43.6	11	36.8	12	25.8	54.1
People not knowing where to go for the services they need	13	24.6	9	38.9	10	37.7	15	18.4	56.2
Infant mortality	16	13.1	14	25.5	17	24.1	16	15.3	65.9
Emergency and ambulance services	17	10.3	16	21.7	13	32.3	10	33.6	105.7

AIDS = acquired immunodeficiency syndrome

*P = .584

TABLE 6.—*Perception and Ranking of Health Care Problems, by Residence*

Health Care Problem	Residence of Family: Urban Rank	Urban %	Rural Rank	Rural %	χ^2 P<.001
Drug abuse	1	65.2	4	47.7	49.6
Drunk driving	3	64.6	5	47.6	115.4
Cost of medical malpractice insurance	5	55.3	6	42.5	30.3
Child abuse	7	49.8	8	30.6	85.4
Pregnant women not getting prenatal medical care	10	36.4	12	21.4	54.9
People who have AIDS	11	35.7	13	14.8	114.9
Teen suicide	12	35.0	15	12.9	153.1

AIDS = acquired immunodeficiency syndrome

school education considered the lack of prenatal care for pregnant women to be more important than did the other groups. Overall, there is a surprisingly high degree of uniformity across the three educational groups.

Employment of Main Wage Earner

The perceptions of health issues by the employment status of the main wage earner in the interviewed household are seen in Table 4. Those not in the labor force tended to give lower ratings for all of the problems—this is due to the high proportion of the retired elderly in this employment category. The results show that the unemployed have different perceptions of the problems than do the other two groups. Teenaged pregnancy was rated a major problem by 64.9% of the unemployed, which gave that problem the second ranking; AIDS was rated a major problem by 47.4% of the unemployed, which gave that problem the seventh ranking; and teenage suicide was rated a major problem by 39.1% of this group, which ranked it tenth. All three of these rankings are substantially higher than those given these problems by the other groups. Only 34.4% of those not employed rated the cost of medical malpractice a major problem, far below the other two groups.

Ethnicity

There are large differences between anglos and ethnic minorities in their perceptions of Arizona's health care problems. The cost of health care was seen as a major problem by 63.1% of anglos, which earned it the number one ranking. It was ranked as the third or fourth highest problem by Latinos, African Americans, and Native Americans. The cost of medical malpractice insurance was seen as a serious problem by 56.6% of the anglos, ranking it fourth. Only 36.7% of Latinos, 35.2% of African Americans, and 42.8% of Native Americans rated this a major problem, and so it was ranked between 7 and 12 by these groups. Conversely, drug abuse, drunk driving, the number of people with no health insurance, teenaged pregnancy, and emergency and ambulance services were rated as more serious problems by these three groups than they were by anglos (Table 5).

There are also some differences within minority groups. Latinos and African Americans rated four issues as more serious than did anglos and Native Americans: lack of services for the old and frail, people with AIDS, people not knowing where to go for services, and infant mortality.

Residence

A comparison of rural with urban perceptions is seen in Table 6. Drug abuse, drunk driving, people with AIDS, teenaged suicide, the cost of medical malpractice insurance, child abuse, and lack of prenatal care for pregnant women are seen as more serious problems in the urban counties than in the rest of the state. There was substantial agreement among the three groups on the remaining ten issues.

Household Income

The poor perceive drug abuse, teenaged pregnancy, lack of prenatal care for pregnant women, and people not knowing where to go for services as more serious problems than do other income groups in Arizona (Table 7). The nonpoor are the most concerned with the cost of medical malpractice insurance. This was seen as a major problem by 59.5% of the nonpoor, which gave it the number four ranking. Only 40.6% of the poor and 44.2% of the nearly poor rated the cost of medical malpractice insurance a major problem, which gave it a rank of between six and ten for these groups. The nearly poor are the most concerned with the number of people with no health insurance. There is a high degree of agreement among the three income groups on the remaining issues.

The various subgroups revealed significant differences in their distribution of problem ratings for 96 of the 102 comparisons. When the proportion that rated a problem as major was used to assign a rank ordering to the problems, however, there was a surprisingly high level of agreement across the subgroups. For example, drug abuse was rated the highest or second highest problem by 16 of 18 subgroups, the cost of health care was rated as one of the top three problems by 15 of 18 subgroups, and drunk driving was rated the second or third highest problem by 11 of 18 subgroups.

Discussion

Results of this survey reveal patterns of common concerns and systematic differences among demographic subgroups within Arizona. Social problems (drug abuse, drunk driving, and teenaged pregnancy) and problems of the economics of health care (high cost of health care, the uninsured, and the cost of medical malpractice insurance) were consistently at the top of the rank ordering of the public's perceptions of major health care problems. There is, however, variation in the extent to which these issues are seen as serious problems. Elderly and rural residents tend to view these problems as less serious than younger and urban respondents, while the poor view these problems as more serious.

The issue with the greatest variation was the cost of medical malpractice insurance. Respondents who were between 40 and 64 years old, with more than a high school education, employed, anglo, urban, and not poor were far more likely to view the cost of medical malpractice insurance as a serious

TABLE 7.—*Perception and Ranking of Health Care Problems, by Income*

	Household Income						
	Poor		Nearly Poor		Nonpoor		χ^2
Health Care Problem	*Rank*	*%*	*Rank*	*%*	*Rank*	*%*	*P<.001*
Drug abuse	1	71.5	2	64.0	2	61.3	32.6
People with no health insurance	5	57.8	4	57.9	5	53.8	17.9
Teenaged pregnancy	3	63.9	3	60.2	6	50.1	40.2
Cost of medical malpractice insurance	10	40.6	6	44.2	4	59.5	42.5
Pregnant women not getting prenatal medical care	9	41.7	11	35.1	10	32.6	24.9
People not knowing where to go for the services they need	11	38.6	13	29.4	13	22.9	55.1

problem than were other respondents. One interpretation of this finding is that communications efforts by the medical community to make the public aware of the problems of the cost of medical malpractice insurance have successfully reached those audiences that are closest to the medical community in demographics but have not been as successful in reaching the broader population.

In contrast, the results show that the general public in Arizona is less concerned with the lack of specific clinical services for high-risk groups—the old and frail, pregnant women, people with AIDS, suicidal teenagers, and abused children. The public is not uniform in these views: anglo, rural, and nonpoor respondents were less concerned with these issues than minority, urban, and poor respondents. This is probably a reflection of both a greater need in the minority, urban, and poor communities for these services and the lack of financial access to these services in poorer communities.

These results have a variety of implications for physicians and other policymakers. They can be interpreted to indicate that the public wants to see stronger efforts to reduce and prevent behaviors such as drug abuse, drunk driving, and teenaged pregnancy. While these results cannot predict if there is more support for public education and prevention programs aimed at these problems than there is for tougher law enforcement, clearly the public wants more effort addressed to these issues.

These results also indicate that controlling the costs of health care and assuring adequate insurance coverage for the entire population are perceived as more important than the specific funding of programs for high-risk or high-need groups. There continues to be strong support in Arizona for allowing uninsured working people to buy into the state's Medicaid program and less support for the creation of a risk pool for nonpoor, medically uninsurable persons or for the expansion of programs for the chronically mentally ill. Given limited government budgets and the many unmet community needs, data such as these can help policymakers target funding expansions.

These results also can serve to inform advocates as to the public's perceptions of health care needs. National attention has been focused on drug abuse and drunk driving by a variety of campaigns; the results of this survey may be a reflection of successful mass media campaigns. In an interest-group democracy, such public opinion is effective in shaping policy. Advocates of malpractice reform can use the public's perception of their issue to garner support for reform; at the same time, broader educational efforts may be necessary if public support is thought to be essential for reform.

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Conferences and Reviews

Upper Gastrointestinal Tract Hemorrhage

Discussant
LOREN LAINE, MD

This discussion was selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from a transcription, it has been edited by Nathan M. Bass, MD, PhD, Associate Professor of Medicine, under the direction of Lloyd H. Smith Jr, MD, Professor of Medicine and Associate Dean in the School of Medicine.

FLOYD C. RECTOR, MD*: *Acute upper gastrointestinal tract hemorrhage is one of the commonest medical emergencies encountered in clinical practice. Although considerable progress has been made in endoscopic diagnoses and treatment, hemodynamic assessment and support remain the mainstays of successful therapy. As an investigator active in the development and evaluation of therapeutic approaches to the problem of upper gastrointestinal tract hemorrhage, Loren Laine, MD, of the University of Southern California (USC) School of Medicine, brings a wealth of experience and insight to his review of this important topic.*

LOREN LAINE, MD†: Upper gastrointestinal (GI) tract hemorrhage remains a major health problem in the United States today, necessitating more than 300,000 hospital admissions annually. In this review, I provide an update on the approach to the management of upper GI tract hemorrhage from the initial assessment to diagnosis and treatment.

Initial Assessment

The most important initial step in a patient presenting with upper GI tract hemorrhage is assessing the hemodynamic state—blood pressure, heart rate, and postural changes. Palpating the distal extremities can be likened to a "poor person's Swan-Ganz catheter"—the extremities of patients with major upper GI tract hemorrhage will be cool because of the peripheral vasoconstriction that occurs with hypovolemia. Too often physicians make the mistake of relying primarily on a patient's hematocrit value while paying little attention to the vital signs. The hematocrit is a poor indicator of the severity or rapidity of an acute bleeding episode. People bleed whole blood. Thus, if a patient's hematocrit is 0.45 (45%), and a third of the blood volume is lost in five minutes, the hematocrit will still be about 0.45. Studies in which healthy volunteers had 15% to 20% of their blood volume removed in about 10 minutes show that the hematocrit takes as long as 72 hours to equilibrate.[1] Patients with an acute, severe bleeding episode typically get to a hospital quickly, and their hematocrit often has not yet fallen greatly. A patient presenting with a systolic blood pressure of 80 mm of mercury and a hematocrit of 0.40 is of far greater concern than one who comes in with a hematocrit of 0.15 and normal vital signs.

Prognosis

About 80% of patients with upper GI tract hemorrhage stop bleeding spontaneously and generally have an uneventful recovery with relatively low morbidity and mortality. Mortality in patients with this disorder is said to be about 10%. Remarkably, this has remained relatively constant over the past 30 to 50 years. Following are some of the reasons the outcome in these patients has not improved:

- Patients presenting with upper GI tract bleeding today are older than they were 50 years ago. Only a small percentage of the patients presenting with bleeding 40 to 50 years ago were older than 60 years; now perhaps half of these patients are older than 60.[2] With this increase in age comes an increase in the number of concurrent illnesses and, as a result, a higher mortality. Patients with upper GI tract hemorrhage usually do not die of exsanguination but rather of worsening of their underlying illness during or after a bleeding episode.
- Most patients with upper GI tract hemorrhage do well without specific therapy or intervention. Therefore, showing a significant improvement is difficult. Successful treatment in high-risk patients is the key to improving outcome, but any improvement in this small group is diluted when all patients with upper GI tract bleeding are considered together.
- Most important, no effective nonsurgical treatment has been available in the past. Without such therapy, the outcome in these patients was unlikely to improve.

Various clinical factors provide prognostic information about the course of a patient presenting with upper GI tract hemorrhage.[3] Patients whose bleeding begins while they are already in hospital for another medical problem—cardiac disease or cancer, for instance—have about a fourfold increase in mortality.[3,4] As mentioned earlier, the combination of upper GI tract hemorrhage and other serious illness is associated with an increase in mortality. Patients presenting with both hematemesis of red blood and hematochezia and patients with hypotension have a mortality higher than those with other clinical presentations of bleeding. Patients with persistent or recurrent bleeding and those with ongoing transfusion requirements—an indicator of persistent or

*Professor and Chair, Department of Medicine, University of California, San Francisco, School of Medicine.

†Associate Professor, Department of Medicine, Division of Gastrointestinal and Liver Diseases, University of Southern California School of Medicine, Los Angeles.

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Reprint requests to Loren Laine, MD, Department of Medicine, Division of Gastrointestinal and Liver Diseases, USC School of Medicine, 2025 Zonal Ave, Los Angeles, CA 90033.

ABBREVIATIONS USED IN TEXT

GI = gastrointestinal
NIH = National Institutes of Health
NSAID = nonsteroidal anti-inflammatory drug
USC = University of Southern California

recurrent bleeding—also have a higher morbidity and mortality.

Upper Versus Lower Gastrointestinal Tract Hemorrhage

We must first determine if the source of gastrointestinal bleeding is in the upper or lower GI tract. Vomiting of red blood or coffee-ground emesis (hematemesis) clearly indicates an upper GI tract source. Melena (black, tarry stool) usually suggests an upper GI tract hemorrhage, and hematochezia (bright red blood through the rectum) is usually from a lower GI tract site. The color does not relate directly to the location of the bleeding site, however; rather, it relates to the length of time the blood remains in the GI tract. Blood from rapidly bleeding lesions in the esophagus or stomach may move through the gut quickly and still be bright red on egress from the rectum. Studies in which blood was instilled at various levels of the GI tracts of volunteers show that hematochezia may result when blood has remained in the gut for eight hours or less.[5] On the other hand, blood must remain in the GI tract for more than 14 hours before melena will develop.[5] Thus, although unusual, hemorrhage from the proximal colon can present as melena if the transit time is slow. If a patient has hematochezia and hemodynamic instability, do not automatically assume that the patient is bleeding from the lower GI tract. Patients with hematochezia and hemodynamic evidence of major bleeding should have an upper endoscopy before the more arduous evaluation of the lower GI tract is undertaken.

Aspiration through a nasogastric tube also has frequently unrecognized pitfalls in establishing the site of gastrointestinal bleeding. Assuming there is no contamination from outside the GI tract such as epistaxis or hemoptysis, the nasogastric aspirate is clearly diagnostic when gross blood or "coffee grounds" are present. Testing the aspirate for occult blood is not of value in a patient with acute bleeding. A normal nasogastric aspirate, however, does not rule out an upper GI tract source of bleeding. As many as 15% of patients with active upper GI tract bleeding have a normal nasogastric aspirate.[6] This probably is seen most commonly with duodenal ulcers. Physicians often suggest that a nasogastric aspirate which is not bloody and appears bilious absolutely rules out a source of bleeding proximal to the second portion of the duodenum. Unfortunately, a physician's impression about the presence of bile in the nasogastric aspirate will be correct in only about 50% of cases.[7]

Auscultating the bowel sounds also may help distinguish between an upper and lower GI tract hemorrhage. Gut motility is increased by intraluminal blood, and this leads to an increase in bowel sounds in patients with bleeding from the upper GI tract.

Blood urea nitrogen levels are classically elevated in patients with upper GI tract bleeding. This increase may reflect prerenal azotemia due to hypovolemia or it may relate to the absorption of a large amount of protein from blood in the small intestine. Instilling blood into the upper small intestine of volunteers can lead to a rise in blood urea nitrogen levels, but no rise is seen when blood is placed in the colon.[8]

Empiric Medical Therapy

A variety of therapies are given to patients with upper GI tract hemorrhage, but none have proved to be effective in stopping bleeding or preventing recurrent bleeding.

Older textbooks report that lavage stops bleeding in 75% of cases. But bleeding stops spontaneously 75% to 80% of the time, and no good evidence exists that lavage plays a role in stopping upper GI tract hemorrhage. Iced saline solution is usually recommended for lavage. Studies in dogs with experimentally induced ulcers indicate, however, that results with lavage are no better and may even be worse at temperatures of 0°C to 4°C.[9] Nasogastric lavage does have a role in these patients: it can document an upper GI tract source of bleeding, and it allows better visualization of the upper GI tract at endoscopy by removing blood and clots.

Patients with bleeding from the upper GI tract frequently receive histamine H_2-receptor antagonists, antacids, or both. Again, numerous studies have failed to document a clear benefit in stopping bleeding or preventing recurrent bleeding. A meta-analysis of studies evaluating the use of cimetidine in patients with this disorder did suggest a possible slight benefit of using H_2-receptor antagonists in the subset of patients with bleeding gastric ulcers. A clinical study aiming to document this improvement would require 10,000 or more patients.[10]

Vasopressin should not be used empirically in patients with gastrointestinal hemorrhage. Its use in those with variceal bleeding will be discussed later. The use of intravenous somatostatin—which is not available in the United States—has shown mixed results.[11] Promising data have been generated with the use of tranexamic acid, an antifibrinolytic agent.[12]

Diagnosis

The two primary methods of diagnosis for upper GI tract hemorrhage are radiography (upper GI series) and endoscopy. The diagnostic yield of upper endoscopy is superior to that of barium studies; endoscopy should identify the source of bleeding in at least 90% of cases. We like to think that identifying the cause of a problem leads to improved management and outcome. Seven controlled trials, however, of early endoscopy in patients with upper GI tract bleeding, all done more than a decade ago, failed to show a benefit of urgent endoscopy in important outcome variables such as surgical intervention, length of hospital stay, and mortality.[13] Thus, the excellent diagnostic yield of endoscopy was not translated into a clinical benefit for the patients. The reason for this may be that these studies were done before gastroenterologists took advantage of the prognostic and therapeutic usefulness of endoscopy. We are unlikely to alter the outcome unless the diagnostic information obtained is used when making patient-management decisions (for example, when to discharge the patient or when to administer endoscopic hemostatic therapy).

Contrast radiographic studies of the upper GI tract have several disadvantages compared with endoscopy. The upper GI series is less accurate than endoscopy; lesions missed include gastric ulcers, Mallory-Weiss tears, erosive and hemorrhagic "gastritis," and varices. In addition, contrast studies do not show active bleeding or stigmata of hemorrhage,

TABLE 1.—*Sites of Bleeding in 445 Consecutive Patients Presenting With Major* Upper Gastrointestinal Tract Hemorrhage at Los Angeles County-University of Southern California Medical Center*

Site of Bleeding	*Patients, No. (%)*
Duodenal ulcer	120 (27)
Gastric ulcer	57 (13)
Varices	137 (31)
Mallory-Weiss tear	60 (13)
Erosive or hemorrhagic gastritis	14 (3)
Erosive esophagitis	8 (2)
Vascular malformations	5 (1)
Prolapse gastropathy	3 (1)
Gastric cancer	3 (1)
Other	5 (1)
Not identified	33 (7)

*Systolic blood pressure 90 mm of mercury or less, heart rate 110 per minute or more, or orthostatic change in systolic blood pressure of 20 mm of mercury or more or in heart rate of 20 per minute; transfusion of 2 units in 12 hours; or drop in hematocrit of 6% in 12 hours.

so lesions identified on upper GI series can only be assumed to be the source of bleeding. Finally, the use of barium contrast is contraindicated in patients with upper GI tract hemorrhage because it may interfere with subsequent studies such as angiography or endoscopy.

The major disadvantage of upper endoscopy is its cost. Endoscopy is generally three to four times more expensive than an upper GI series. If endoscopy does not improve the outcome in patients with upper GI tract bleeding, then we are not justified in doing endoscopy in them. Recent studies indicate, however, that early endoscopy can improve patient care and decrease costs. Endoscopic findings can be used prognostically to help decide on the level of patient care and time of discharge, and endoscopic hemostatic therapy is beneficial in patients at high risk for persistent or recurrent bleeding.

Causes and Treatment of Upper Gastrointestinal Tract Hemorrhage

Table 1 lists the sources of bleeding in 445 consecutive patients presenting to Los Angeles County-USC Medical Center with clinically severe upper GI tract hemorrhage. About 40% of patients bled from ulcers (with duodenal ulcers twice as common as gastric ulcers), and 30% bled from esophagogastric varices. Series from hospitals with fewer patients with alcoholic liver disease generally show a lower prevalence of variceal bleeding (about 10%) and a greater number of bleeding ulcers (usually 50% or more). Although many series list erosive and hemorrhagic "gastritis" as a common cause of bleeding, in our experience, this is an uncommon cause of clinically severe upper GI tract bleeding.

Mallory-Weiss Tears

Mallory-Weiss tears, seen most commonly in patients with alcoholism, are shallow lacerations that are usually on the gastric side of the gastroesophageal junction. Most Mallory-Weiss tears stop bleeding spontaneously, and hemorrhage rarely recurs. Generally no intervention is required, and supportive therapy is sufficient. A patient with persistent bleeding from a Mallory-Weiss tear can be treated successfully with endoscopic therapy. If this is unsuccessful or unavailable, angiographic therapy with embolization or vasopressin infusion through the left gastric artery also can be effective. Surgical therapy is rarely needed to oversew a bleeding Mallory-Weiss tear.

TABLE 2.—*Endoscopic Hemostatic Therapy*

Thermal Methods	*Injection Therapy*
Laser photocoagulation	Absolute ethanol
Argon laser	Sclerosing agents, such as polidocanol
Nd:YAG laser	Epinephrine
Electrocoagulation	Saline solution
Monopolar	
Bipolar or multipolar	
Heater probe	

Nd:YAG = neodymium yttrium aluminum garnet

Peptic Ulcers

Peptic ulcers are the most common cause of serious upper GI tract hemorrhage. The appearance of the ulcer at endoscopy provides important prognostic information. Ulcers may have a clean base, they may have stigmata of recent hemorrhage (flat pigmented spot, adherent clot, or nonbleeding visible vessel), or they may be actively bleeding. Ulcers with a clean base have a 1% incidence of recurrent bleeding, similar to that of a nonbleeding Mallory-Weiss tear. Flat pigmented spots portend rebleeding in 7% to 8% of cases, and patients whose ulcers have adherent clots rebleed about 20% of the time. Bleeding recurs in 40% of patients with nonbleeding visible vessels, and about a third will require urgent surgical therapy for bleeding if not treated endoscopically. Patients with active bleeding identified at endoscopy have the worst outcome—more than half may require urgent intervention. Patient management can therefore be guided by the features of the ulcer identified at endoscopy.

I think that patients with nonbleeding Mallory-Weiss tears or clean-based ulcers can be discharged home after being stabilized, thereby decreasing hospital costs and justifying the expense of early endoscopy. Patients with flat pigmented spots or adherent clots probably should be observed in the hospital, but no specific intervention is required. On the other hand, patients with nonbleeding visible vessels or active bleeding are at high risk for further bleeding and often require surgical intervention. This is the subset of patients in whom effective alternatives to emergency surgical treatment are needed to decrease the morbidity and mortality associated with upper GI tract hemorrhage. The recent introduction of endoscopic hemostatic therapy appears to have provided an effective nonsurgical therapy for patients with active bleeding or nonbleeding visible vessels.

Endoscopic Hemostatic Therapy

> *Those diseases which medicines do not cure*
> *the knife cures*
> *Those which the knife cannot cure*
> *cautery cures*
> *And those which cautery cannot cure*
> *are reckoned to be wholly incurable.*
>
> HIPPOCRATES [5TH CENTURY BC]

Thermal methods. Various thermal methods for endoscopic hemostasis are available (Table 2). Laser photocoagulation was among the first methods studied in patients with upper GI tract bleeding. Although effective in some clinical trials, laser therapy is no longer generally used to treat this

TABLE 3.—*Controlled Trial of Multipolar Electrocoagulation in Patients With Active Upper Gastrointestinal Tract Bleeding**

Variable	Sham Therapy, n=23	Coagulation, n=21	P value <.05
Hemostasis, %	13	90	†
Transfusions, units	5.4	2.4	†
Emergency intervention, %	57	14	†
Hospital stay, d	7.2	4.4	†
Hospital cost, $	7,550	3,420	†
Mortality, %	13	0	

*From Laine.[17]
†P<.05 for sham therapy versus electrocoagulation.

disorder for a number of reasons: laser units are extremely expensive; they are not portable (so the unit cannot be taken to a critically ill patient in an intensive care unit or emergency department); yttrium-aluminum-garnet lasers cause considerable tissue injury, which increases the theoretic risk of perforation; in animals, laser therapy is less successful than the contact devices discussed later in coagulating larger arteries; and, finally, laser requires more technical skill than other hemostatic methods.

Monopolar electrocoagulation is available in most gastroenterology and surgical units, and three clinical trials suggest clinical efficacy in these patients. Because of the substantial tissue injury induced by monopolar electrocoagulation, however, and the risk of perforation, most experts do not recommend its use.

The National Institutes of Health (NIH) held a consensus conference on therapeutic endoscopy for bleeding ulcers in 1989,[14] and the panel's conclusion was that the two "most promising techniques" for endoscopic hemostasis were bipolar or multipolar electrocoagulation and the heater probe. Both are contact thermal devices that involve tamponade of the bleeding lesion combined with the application of heat. They are portable and relatively inexpensive ($6,000), and, in animals, both are effective at coagulating all arteries 2 mm or less in size.[15] (Swain and co-workers found that the artery size in 27 patients with gastric ulcers with visible vessels that rebled ranged from 0.1 to 1.8 mm.[16])

Clinical trials from USC have documented the efficacy of multipolar electrocoagulation in patients with clinically severe upper GI tract hemorrhage and endoscopic evidence of active bleeding or an ulcer with a nonbleeding visible vessel (Tables 3 and 4).[17,18] Trials from Taiwan and California also appear to indicate that the heater probe is beneficial in a similar group of patients (Table 5).[19,20]

TABLE 4.—*Controlled Trial of Multipolar Electrocoagulation in Patients Who Have Ulcers With Nonbleeding Visible Vessels**

Variable	Sham Therapy, n=37	Coagulation, n=38	P value <.05
Rebleeding, %	41	18	†
Transfusions, units	3.0	1.6	
Emergency operation, %	30	8	†
Hospital stay, d	6.2	4.3	†
Hospital cost, $	5,730	3,790	†
Mortality, %	0	3	

*From Laine.[18]
†P<.05 for sham therapy versus multipolar electrocoagulation.

TABLE 5.—*Controlled Trial of Heater Probe in Patients Who Have Ulcers With Active Bleeding or Nonbleeding Visible Vessels**

Variable	Patients: Control, n=32	Patients: Heater Probe, n=32	P value <.05
Hemostasis, %†	20	93	‡
Further bleeding, %	72	22	‡
Transfusions, units	3.5	1.3	
Operation for bleeding, %	41	3	‡
Mortality, %	9	3	

*From Jensen et al.[20]
†Patients with active bleeding.
‡P<.05 for control versus heater probe.

Injection therapy. Although the trend in medicine is toward more expensive and "high-tech" forms of therapy, the treatment of upper GI tract bleeding is moving in the opposite direction. We have gone from $100,000 laser units to $6,000 bipolar or multipolar electrocoagulation and heater probe units to possibly the simplest form of therapy: injection therapy. Injection therapy requires only a retractable sclerotherapy needle (which fits through the biopsy channel of an endoscope) and a solution to be administered directly into the base of an ulcer or other bleeding lesion. Agents that are commonly used include absolute ethanol, sclerosing agents such as polidocanol, and epinephrine (1:10,000). Controversy exists regarding the mechanism of epinephrine in hemostasis. Some think that the vasoconstrictive effect of epinephrine is important in hemostasis, but others suggest that epinephrine works by tamponade due to the volume effect alone. The latter concept is supported by a recent preliminary report from Taiwan showing that injection with a normal saline solution is as effective as using epinephrine or absolute ethanol. The results of six clinical trials comparing injection therapy with no endoscopic therapy indicate that injection therapy improves the outcome in patients with bleeding ulcers (Table 6).[21,22]

Guidelines for endoscopic therapy. Endoscopic hemostatic therapy should now be considered standard therapy in the treatment of a subset of patients with nonvariceal upper GI tract hemorrhage. The 1989 NIH consensus conference on therapeutic endoscopy concluded that patients with clinical evidence of a major bleed and endoscopic evidence of an ulcer with active bleeding or a nonbleeding visible vessel are at high risk for persistent or recurrent bleeding and should receive endoscopic hemostatic therapy.[14] Comparisons of different modalities are now appearing, and, based on the information available, bipolar or multipolar electrocoagulation, heater probe, and injection therapy should be considered roughly comparable for the treatment of nonvariceal upper GI tract bleeding.

Esophageal Varices

Bleeding esophageal varices have a higher morbidity and mortality than any other source of upper GI tract hemorrhage. Bleeding esophageal varices represent just the tip of the alcoholism "iceberg" in the United States. We can estimate that cirrhosis develops in about 15% of all persons with chronic alcoholism, and varices develop in perhaps two thirds of those with cirrhosis. Furthermore, only a third or less of patients with varices will bleed from them. Once

TABLE 6.—*Controlled Triol of Injection Theropy for Potients With Upper Gostrointestinol Troct Hemorrhoge Due to Ulcers**

Voriable	Treotment: Control, n = 55	Treotment: Injection, n = 58	P value <.05
Transfusions, units	2.8	0.4	†
Emergency operation, %	34	5	†
Hospital stay, d	16	12	†
Mortality, %	7	4	

*From Panés et al.22
†P<.05 for control versus injection therapy.

bleeding develops, however, patients do poorly. The mortality of a bleeding episode is in the range of 15% to 40%, and the long-term survival is similar to that of many cancers—that is, 60% to 80% may die within one to four years. Mortality rates probably are closely related to the severity of the underlying liver disease.

Three forms of nonsurgical therapy are generally used in the treatment of bleeding esophageal varices: intravenous vasopressin, balloon tamponade, and esophageal sclerotherapy. Although intravenous vasopressin is used frequently, clear-cut evidence supporting its benefit from placebo-controlled trials is not available. An older trial of posterior pituitary extract showed a decrease in bleeding by nasogastric aspirate but no change in a rather abysmal survival,[23] whereas a more recent study from Stanford showed no benefit of using vasopressin.[24] In addition, vasopressin use is associated with serious complications including myocardial ischemia and infarction, and patients occasionally may die of this treatment. Adding nitrates to vasopressin therapy may decrease the adverse cardiovascular effects.

Balloon tamponade (the Sengstaken-Blakemore tube has an esophageal and gastric balloon, and the Linton-Nachlas tube has only a gastric balloon) may arrest bleeding at least temporarily in as many as 85% to 90% of cases but does not alter survival.[25] In addition, patients may die of complications of the balloon tamponade treatment itself.

A large number of patients—as many as 50%—with liver disease, previously documented varices, or both who present with upper GI tract hemorrhage are bleeding from a nonvariceal source. Therefore, patients with liver disease, known varices, or both who are admitted with upper GI tract bleeding should undergo upper endoscopy before therapy aimed at variceal bleeding is instituted. Patients should not receive treatment such as vasopressin or balloon tamponade that is potentially lethal and of questionable efficacy unless varices have been documented.

Endoscopic sclerotherapy is an effective nonsurgical treatment of variceal bleeding.[26] A retractable sclerotherapy needle is passed through the biopsy channel of the endoscope, and one of various sclerosing agents is injected directly into the varix or into the mucosa alongside the varix. Sclerotherapy leads to acute inflammation, necrosis, thrombosis, and fibrous repair with eventual obliteration of the variceal channels. Controlled clinical trials of the effects of acute sclerotherapy—defined as an evaluation more than two to six weeks from the index bleed—suggest that sclerotherapy decreases the number of rebleeding episodes and transfusion requirements but does not clearly improve mortality. Long-term sclerotherapy requires serial endoscopic sclerotherapy sessions to obliterate all esophageal varices. Thereafter, patients return for endoscopic surveillance every three to six months, and any recurrent varices are treated. Episodes of rebleeding are considerably decreased in almost all trials of long-term sclerotherapy, and mortality also is significantly decreased in half the trials. Thus, in some studies, endoscopic sclerotherapy will improve survival, a finding not reported in older controlled trials of portocaval shunts.

Any patient with liver disease or a history of varices who presents with bleeding should undergo endoscopy before therapy is instituted. If esophageal varices are the cause of the bleeding, then the endoscopist should do sclerotherapy at the time of the diagnostic endoscopy, rather than withdrawing the endoscope and administering treatments such as vasopressin or balloon tamponade, which are inferior to sclerotherapy and potentially lethal.

Sclerotherapy is associated with a notable incidence of complications. Toxic agents are injected into varices and the esophageal mucosa, leading to both local complications (such as ulceration, bleeding, strictures, or perforation) and distant complications (such as pleural effusions, the adult respiratory distress syndrome, pericarditis, portal vein thrombosis, bacteremia, spinal cord paralysis, or brain abscess).

A new form of endoscopic treatment of esophageal varices has recently been devised: band ligation.[27] The aim of this treatment is to establish a form of therapy at least as effective as sclerotherapy with fewer complications. In principle, the technique of band ligation of internal hemorrhoids has been adapted to ensnaring esophageal varices with subsequent inflammation, fibrous repair, and it is hoped, the obliteration of varices. Preliminary results suggest that this technique may decrease the incidence of complications (especially esophageal strictures) without a decrease in efficacy compared with sclerotherapy.

Hemorrhagic and Erosive 'Gastritis'

"Gastritis" is among the most loosely used terms in medicine. To be precise, gastritis is a histologic diagnosis that requires a gastric mucosal biopsy specimen which shows microscopic evidence of inflammation. No evidence exists to indicate that histologic gastritis has any relation to upper GI tract hemorrhage or other gastrointestinal symptoms. Hemorrhagic and erosive gastritis refers to endoscopically visualized lesions that may cause upper GI tract bleeding.[28] Hemorrhagic gastritis has the appearance of petechiae or "blood under plastic wrap," and erosions are small, flat, or minimally depressed white-based lesions. There is no definite association between these macroscopic abnormalities and histologic gastritis.

The hemorrhagic lesions represent blood in the mucosa beneath the epithelial layer, whereas erosions are breaks in the mucosa that do not extend into the submucosa. Once a defect extends beyond the mucosa into the submucosa or deeper, it is an ulcer. Thus, the differentiation between an erosion and an ulcer is a histologic one, and endoscopists may not always be able to distinguish between the two. Because all blood vessels of substantial size are in the submucosa or deeper, hemorrhagic or erosive gastritis will generally not cause serious upper GI tract bleeding. Ulcers, on the other hand, will cause serious bleeding when they erode into larger arteries below the level of the mucosa.

Hemorrhagic and erosive gastritis generally does not occur de novo but is seen in certain clinical situations.[28] The most important predisposing conditions are stress, drug ingestion, such as nonsteroidal anti-inflammatory drugs (NSAIDs), and alcohol abuse.

Stress gastritis occurs only in extremely sick patients: patients with major trauma including major operations; patients with burns greater than a third of their body surface area; patients with major intracranial disease, such as those in neurosurgical intensive care units; and severely ill medical patients—those with ventilator dependency, sepsis, or coagulopathy. Almost all of these patients have endoscopic evidence of gastritis if they are examined within 12 to 24 hours of admission. The major concern in these patients is the development of hemorrhage from stress gastritis or stress ulceration. Generally the lesions in stress gastritis are superficial mucosal hemorrhages and erosions, but occasionally an ulcer may develop. As discussed, major bleeding in a patient with stress presumably indicates that an erosion has deepened to become an ulcer. If severe bleeding develops in these extremely ill patients, the mortality is high because of the underlying illness.

In recent years, the incidence of bleeding from stress gastritis appears to have decreased dramatically. This may be due in large part to better intensive care techniques in critically ill patients. Pharmacologic prophylaxis of stress gastritis bleeding also is commonly used. The use of antacids, H_2-receptor antagonists, or sucralfate appears to decrease the amount of bleeding from stress gastritis. These decreases, however, are generally in occult bleeding or overt blood in the nasogastric aspirate. Clear evidence of a decrease in clinically substantial bleeding or mortality is generally lacking from the controlled clinical trials.

The use of aspirin and NSAIDs is the most important cause of gastric injury in the United States and Europe. Taking two aspirin tablets will lead to gastric hemorrhagic lesions in virtually 100% of subjects, and two tablets every six hours for one day will cause erosions in almost all subjects. Clearly some adaptation must take place because not all patients on long-term NSAID or aspirin therapy have gastric lesions. However, 40% to 50% of patients ingesting aspirin or NSAIDs regularly will have erosions, and as many as 15% to 20% will have gastric ulcers. Also of interest are recent reports from the United Kingdom and the US suggesting that, especially in older patients, the use of NSAIDs may increase the incidence of not just ulcers but also ulcer complications such as bleeding, perforation, and death.[29]

Alcohol abuse is another important cause of hemorrhagic and erosive gastritis. At Los Angeles County-USC Medical Center, we prospectively evaluated 170 actively drinking patients with chronic alcoholism who presented with upper GI tract bleeding. About 20% had evidence of hemorrhagic or erosive gastritis, with hemorrhagic lesions being twice as common as erosions. Experimental evidence exists suggesting that alcohol-induced gastric injury may be worse in patients with underlying portal hypertension.[30] When rats with portal hypertension have alcohol instilled into their stomachs, the gastric injury is greater than in rats without portal hypertension given the same agent.

Conclusion

Upper gastrointestinal tract hemorrhage is a common problem with a long list of possible causes. Assessing the hemodynamic state is the first priority in patients presenting with this disorder. Only after efforts at stabilization have begun should attempts be made to establish the source of bleeding. Endoscopy provides an excellent diagnostic yield, and, although older studies showed no benefit from early endoscopy, more recent data suggest that endoscopy is beneficial in determining appropriate patient management and allowing endoscopic hemostatic therapy to be given. The effects of the measures on outcome need to be evaluated further.

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Primary Ciliary Dyskinesia

LAURIE LE MAUVIEL, DO, *Minneapolis, Minnesota*

This paper was chosen as the runner-up in THE WESTERN JOURNAL OF MEDICINE's 1991 Medical Student Writing Competition. The contest was open to all students attending medical schools in the West and will be repeated annually.

LINDA HAWES CLEVER, MD
Editor

Primary ciliary dyskinesia represents a group of heritable disorders of cilia and sperm affecting between 1 in 15,000 and 1 in 30,000 persons. Those affected lack measurable mucociliary clearance and suffer the constant misery of rhinorrhea and chronic productive cough. Because mucociliary clearance constitutes one of the respiratory system's major lines of defense, these patients are vulnerable to chronic sinusitis, bronchitis, pneumonia, and otitis media. Left untreated, these problems may progress to bronchiectasis, found frequently in adult patients, or pulmonary hypertension with eventual cor pulmonale. Screening for this disorder includes some simple and inexpensive methods as well as more exotic techniques requiring special camera equipment and an electron microscope to make a definitive diagnosis. Physiotherapy techniques can be taught to patients with primary ciliary dyskinesia and go a long way toward making up for the lack of mucociliary clearance. Vigorous bronchopulmonary toilet and palliative measures may enable these patients to enjoy relatively normal lives.

(LeMauviel L: Primary ciliary dyskinesia. West J Med 1991 Sep; 155:280-283)

Primary ciliary dyskinesia (PCD) is the name that has evolved for a group of disorders caused by microtubular defects in cilia and sperm. This group of disorders was previously known as the immotile cilia syndrome until it was discovered that most of the cilia did move, albeit in an uncoordinated or dyskinetic manner.[1,2] These defects render the cilia in the respiratory tract ineffective in clearing secretions,[1,3] a condition that can lead to sinusitis, repeated pulmonary infections, bronchiectasis, obstruction, and air trapping.[4-7] Dysfunctional cilia in the middle ear leave patients vulnerable to repeated otitis media, and most suffer some degree of hearing loss.[5] Sperm, which contain an identical microtubular arrangement to cilia in their tails, have been shown to be capable of fertilizing an egg[8] but usually lack sufficient motility to reach one.[9,10] The microtubular defects found in PCD have also been shown to cause motility problems in phagocytic cells where microtubules are involved in directed movement to capture pathogens.[11-13]

Primary ciliary dyskinesia is an autosomal recessive disorder thought to affect between 1 in 15,000 and 1 in 30,000 persons.[14,15] The link between PCD and situs inversus, which occurs in about 50% of patients with the disorder,[15] and the precise genetic defect that allows for the great heterogeneity in ciliary ultrastructure found in PCD are still subjects of speculation. The exact chain of mechanochemical events that enable microtubules to cause movement is still unknown, but how the various microtubular defects alter ciliary motion and thus inhibit mucociliary clearance is now understood.[7] More advanced ways of screening for and evaluating the disorder may lead to earlier recognition and treatment that can slow the disease's progression.[6]

History

The study of primary ciliary dyskinesia began with the clinical observation as early as 90 years ago of disease syndromes involving various combinations of pulmonary disease, situs inversus, and male infertility.[16] To date, at least 20 inherited heterogeneous disorders of ciliary ultrastructure have been identified by electron microscopy.[7] The occurrence of situs inversus with bronchiectasis was first reported in 1904 by Siewert. In 1933, Kartagener made a detailed study of 11 persons having sinusitis, bronchiectasis, and situs inversus and was the first to suggest a common pathogenesis.[17] The triad was henceforth known as Kartagener's syndrome. Several reports, including two from the Mayo Clinic, followed[16] with similar observations to Kartagener's. In 1975, Afzelius found, in a study of four men with immotile sperm and repeated respiratory infections, that the sperm microtubules lacked dynein arms.[18] Dynein is a globular protein that contains adenosine triphosphatase activity. Dynein arms form temporary cross-bridges between adjacent peripheral microtubules in cilia and sperm tails producing movement similar to the myosin cross-bridging found in skeletal muscle.[19] The men in Afzelius's study had all suffered from chronic sinus infections, bronchitis, pneumonias, and common colds from childhood and had no measurable mucociliary transport. Three of the men had situs inversus.[18]

Kartagener's syndrome is now considered to nearly always be a subset of primary ciliary dyskinesia.[7] Manifestations of PCD and Kartagener's syndrome overlap with Young's syndrome.[20,21] Young in 1970 described a group of men who had live sperm but obstructive azoospermia, com-

From the College of Osteopathic Medicine of the Pacific, Pomona, California.
Reprint requests to Laurie LeMauviel, DO, Dept of Internal Medicine, Hennepin County Medical Center, 701 Park Ave So, Minneapolis, MN 55415.

bined with chronic sinopulmonary infections.[20] Other studies found similar patients to also have chronic otitis media and bronchiectasis.[22] Young's syndrome differs from PCD in that the cilia and sperm tails are ultrastructurally normal.[21]

Pathophysiology

Cilia are ubiquitous throughout the body, being found in the nose, the paranasal sinuses, the middle ear, the bronchi, the cornea, on the ependyma lining the ventricles of the brain and the spinal cord, and lining part of the epididymus, the female fallopian tubes, and the uterus. Sensory hair fibers such as those of the inner ear and olfactory nerve are modified cilia, but no conclusive evidence links PCD with sensory deficits.[21] Phagocytic cells, while they do not have cilia, do have microtubules that are involved in their directed movement during phagocytosis.[11-13] Cinemicrographic evidence shows that polymorphonuclear leukocytes of patients with PCD take a more tortuous path in rapid movement[11] and show a decreased ingestion of bacteria.[12] The cilia of the ependyma are thought to have little involvement in the movement of cerebrospinal fluid.[21] Reduced fertility or infertility has been reported in some women having PCD,[23] but it is generally thought that a coordinated movement of cilia is not crucial to fertilization of the ovum and implantation.[24-26] The motility of sperm tails relies on microtubules identical to those in cilia, and men with PCD are usually infertile.[9,27] In one reported case, sperm were found to be capable of fertilizing an egg when placed with the egg in vitro,[8] and in another report, a 21-year-old patient having motile sperm had fathered a child.[9]

Cilia are essential for clearing mucus and trapped particles and pathogens from the respiratory tract. It follows that respiratory problems make up the major share of the morbidity suffered by patients with primary ciliary dyskinesia.[6] Mucus travels in a bilayer throughout the respiratory tract, with a periciliary sol or watery phase lying directly against the epithelium and a gel phase layer of thicker, more elastic mucus on top. Rheologic properties of mucus—the elasticity more so than the viscosity—interact with ciliary motion to influence transport rate. Mucus that is too watery, too elastic, or too viscous cannot be efficiently moved by cilia. Deformation of the cilia by the mucus is also needed for mucous transport.[7,21]

In normal cilia, microtubules are found in a nine-plus-two arrangement, with nine doublets arranged peripherally around two singlets enclosed in a sheath in the center. Peripheral microtubules are connected to the center sheath by radial spokes, and adjacent doublets are connected by strands of nexin. One member of each pair of doublets has a pair of dynein arms.[4] These effect sliding of the doublets by means of globular protein heads, each of which has as many as nine heavy chains of protein. Dynein is a protein varying in size from 12S to 22S, depending on the species,[28] and like myosin has ATPase activity. Although functionally similar to myosin, dynein has a greater repertoire of activity. Whereas muscle fibers can only shorten and relax, cilia are able to move in a planar or three-dimensional manner and are even capable of helical strokes.[28,29]

The ultrastructural defects affect the function of the cilia in specific ways. The beat frequency and the waveform of normal cilia determine their proficiency in clearing mucus. Normal ciliary movement might be likened to a gentle gust of wind blowing through a wheat field. The cilia first bend forward and then make a backward sweep with a recovery stroke.[7] Not all the dynein arms operate at once; about half the arms are involved in the effective stroke, and the other half switch on for the recovery stroke.[30] With a dynein deficiency in both arms, the cilia are able only to vibrate or rotate. Radial spoke defects cause a motion of biphasic rotation about a vertical axis like the inside of a washing machine. When microtubules are missing, cilia are limited to a grabbing motion. The mean beat frequency of normal cilia is about 12.5 Hz $\pm$ 1.8 with a normal waveform. The cilia of patients with respiratory disease have a slightly increased beat frequency and normal waveform, and patients with PCD have a beat frequency of about 7.8 Hz $\pm$ 3.2 with a dyskinetic waveform.[7]

Genetic Aspects

The specific microtubular defects of cilia and sperm that cause primary ciliary dyskinesia are inherited by autosomal recessive transmission[15] and are heterogeneous.[31-33] About 70% to 80% of the microtubular defects involve dynein deficiency with one or both arms missing.[7] Other defects include missing microtubules, malarrangement of the microtubules, nexin deficiency, or radial spoke defects.[7,34] The various defects are primary, or present at birth, and generalized, meaning that the cilia throughout the tissues of the body have the same ultrastructural defect. That dynein-deficient patients with PCD usually lack the protein arms both in cilia and sperm tails suggests that the dynein in both is either genetically linked or coded for by the same gene.[8] Reports exist, however, in which patients had either normal ciliated respiratory epithelium and immotile sperm or the reverse.[9,10,35] This may suggest that the spermatozoal and ciliary dyneins are under partially separate genetic control.[8] Some persons have the clinical manifestations of PCD with ultrastructurally normal cilia.[36,37]

The genetic link between situs inversus and PCD is not completely clear. Rott has posed several possibilities. One is pleiotropy, or the finding of one mutation in different phenotypic forms. He suggests the possibility of a shift factor that determines normal orientation of the viscera and that when absent offers the possibility of random orientation. A random determination of visceral rotation during embryonic development would explain why situs inversus is found in about half the patients with PCD.[15]

Afzelius, however, has postulated that the lack of ciliary movement itself leaves the rotation of the embryonic archenteron during embryonic development to chance. The differentiating cells of early vertebrate embryos also have cilia lining the coelomic cavity. Afzelius suggests that these have a fixed beat direction that determines the chirality of the embryonic viscera. He notes that in experiments in which the beating of embryonic cilia of lower animals is stopped by chilling the embryo, situs inversus resulted in a larger-than-expected proportion.[18]

Clinical Manifestations

Repeated upper and lower respiratory tract infections beginning in infancy or early childhood should alert physicians to include PCD in the differential diagnosis.[5-7] Chronic sinusitis, bronchitis, and otitis media are found in nearly all cases.[7,34] Nasal polyps, usually uncommon in children, are found in about 10% of children with PCD and about 75% of adults.[34] Chronic rhinorrhea with constant nose blowing is a

common symptom.[5-7] Most patients suffer from a chronic productive cough and recurring pneumonia. *Hemophilus influenzae* is the most commonly cultured pathogen and with *Neisseria meningitidis* and *Streptococcus pneumoniae* causes most infections.[7,34] *Pseudomonas aeruginosa* is sometimes cultured but not with the frequency found in cystic fibrosis patients.[5] Untreated, these infections can lead to more serious disease. Chronic, untreated sinus infections may lead to brain abscesses, osteomyelitis, or meningitis. The decreased mucociliary clearance leads to mucous plugging and stasis, which can result in bronchiectasis, pulmonary hypertension, and eventually cor pulmonale.[7,34] Many patients require tympanostomy tubes, which are variably successful in clearing up resistant ear infections.[6] Hearing deficits develop in most patients.[34,38]

Chest radiographs of patients with PCD frequently show hyperinflation, bronchial wall thickening, segmental atelectasis, or consolidation. The signs and symptoms are similar to those of cystic fibrosis but less severe and more slowly progressive.[39] Bronchiectasis is most commonly noted in the middle and lower lung lobes and the lingula.[7] Thickening of the nasal mucosa and opacification of frontal sinuses were noted by Levison and co-workers, who also found clubbing in some patients. They also found that most patients showed abnormalities in pulmonary function—usually a reduced expiratory flow rate—with more severely affected patients having a reduced forced vital capacity. Most also have an increased ratio of residual volume to total lung capacity, showing an obstructive pattern with air trapping.[34]

Diagnosis

Primary ciliary dyskinesia needs to be correctly diagnosed as early as possible to rule out treatable diseases or more serious disorders such as cystic fibrosis, hypogammaglobulinemia, α_1-antitrypsin deficiency, or even allergies.[7] Parents of children with PCD can benefit from genetic counseling because PCD is a disorder with potentially serious health consequences and male children may suffer infertility.[34] Early diagnosis also enables physicians to get an early start in teaching the bronchial hygiene that may prevent problems or treating infections before they become serious.[6,7]

Patients with PCD begin having problems early in life but may present to a variety of physicians and other health care professionals at any time in life. Ear, nose, and throat specialists will see children for repeated ear infections, psychologists see the learning disabilities that result from poor hearing, infertility specialists will see adults whose disorders have gone undetected throughout life, and pulmonologists will be called in on cases of repeated pneumonia and resistant presumed asthma.[7]

Selecting from among the numerous methods of diagnosis depends on the patient, the resources available to the physician, and financial considerations, but a history is the place to start. The key points to look for in a patient's history are repeated upper and lower respiratory tract infections since infancy or childhood, chronic sinusitis or rhinorrhea, chronic otitis media with possible hearing deficits, chronic bronchitis in children and bronchiectasis in adults, male infertility, and situs inversus in about 50% of cases.[4-7,34] On physical examination, the aforementioned radiographic evidence and pulmonary function testing may provide clues.[39] Cystic fibrosis and hypogammaglobulinemia should be ruled out by a sweat test and serum immunoglobulin levels, respectively, before proceeding further.[40] The methods of gathering physical evidence vary, but several investigators find determining mucociliary clearance to be the next logical step.[40,41] Because patients with PCD characteristically have impaired mucociliary transport, the more simple and cost-effective saccharin test is appropriate for some patients.[6,42] In the saccharin test, a 1-mm bead of saccharin is placed 1 cm from the most anterior part of the nose on the inferior turbinate. The time between placement of the bead and the patient sensing sweetness is then measured. Normal transit time is between 15 and 19 minutes, with more than 30 minutes considered abnormal. The test is usually terminated after 60 minutes. The drawbacks of the test are that it is subjective and requires the patient's cooperation. The patient's head must be held tilted forward at a 15-degree angle, and the patient must not cough, sneeze, sniff, eat, or drink during the test.[42] Variations on the test solve the subjectivity problem by adding dye to the saccharin or substituting an aerosolized insoluble material such as polystyrene or a radiolabeled substance to be inhaled orally.[3,7,40] Some physicians proceed with ciliary motion analysis in which a brushing is taken from the nasal mucosa. The specimen is taken with a cytobrush and placed on warmed depression slides in a Krebs solution. The motion is examined with an analysis equiphase contrast microscope that magnifies 100 times and is recorded with a gamma camera.[7] The ultrastructure is analyzed under an electron microscope. Unfortunately, many of the diseases from which PCD must be differentiated also cause ultrastructural ciliary defects mimicking PCD. These include differences in microtubular number, orientation, and arrangement and microtubular defects found in patients having chronic infection from bronchitis, sinusitis, cystic fibrosis, or asthma.[7,34,43,44] For this reason, it is important to examine sections containing between 500 and 2,000 cilia and to avoid taking specimens from patients who have had a viral or bacterial infection within the past six weeks.[7,44] With insufficient specimens or poor timing, a clinician may be fooled. Rossman and Newhouse suggest obtaining specimens from at least 20 to 30 randomly chosen sites where most cilia appear immotile to establish the proportion of motile cilia.[7] It is also essential to study the cilia in cross section at least 2 μm above the cell membrane because the center singlets terminate at about 1 μm above the cell surface. Specimens may be taken by brushing or by biopsy, although some investigators consider biopsy unnecessarily traumatic.[40] Sources disagree about the necessity of taking specimens from sites other than the nose—trachea, bronchus, sperm.[7,34]

Management

Bronchopulmonary toilet is a cornerstone of PCD therapy. Patients with primary ciliary dyskinesia are totally reliant on two mechanisms for secretion removal: coughing, which is almost as effective as the mucociliary elevator in removing secretions,[7,45,46] and gas-liquid pumping, which involves patients manipulating their secretions by sucking up or down in the back of their throats. Patients can benefit by clearing secretions by these methods every two to three hours while awake. Physiotherapy, such as postural drainage and percussion, may be helpful on an as-needed basis but are not as effective as cough.[7] A relative innovation in chest physiotherapy, the forced expiration technique, may be taught to these patients. Forced expiration, or the "bovine" or "huff-

ing" cough, is done without glottic closure and applies a shearing force to secretions that aids in expectoration.[45]

A variety of medications are used to relieve patients' symptoms. Various authors suggest the use of saline aerosols and hypertonic saline solution, methylxanthines, guaifenesin, and bromhexine hydrochloride to improve clearance.[5-7,40,45] Obstruction can be relieved with β-agonists. Decongestant use may relieve sinusitis; mucolytics and adequate hydration may keep secretions from becoming too tenacious to move; and rhinorrhea may be relieved with anticholinergic aerosols. Surgical interventions include trimming the inferior turbinate to relieve sinus obstruction or meatal antrostomies, in which larger exits are drilled into the sinuses for mucus to drain through by gravity.[6] Patients with PCD should have a culture-and-sensitivity workup and receive antibiotics at the first sign of infection because the progression of chronic pulmonary infection to bronchiectasis is one of the worst consequences of the disease.[6] Some patients benefit from periodic courses of antibiotics as a preventive measure.[7]

Despite the significant morbidity and discomfort associated with PCD, the disease progresses more slowly than cystic fibrosis and can be slowed even more by educating patients and treating infection promptly. Overall, it has a better prognosis than cystic fibrosis,[5] and these patients may go on to lead relatively normal lives and remain stable for long periods of time.[4,7]

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Epitomes

Important Advances in Clinical Medicine

Emergency Medicine

The Scientific Board of the California Medical Association presents the following inventory of items of progress in emergency medicine. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome, and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, researchers, or scholars to stay abreast of these items of progress in emergency medicine that have recently achieved a substantial degree of authoritative acceptance, whether in their own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Emergency Medicine of the California Medical Association, and the summaries were prepared under its direction.

Reprint requests to Division of Scientific and Educational Activities,
California Medical Association, PO Box 7690, San Francisco, CA 94120-7690

Zidovudine for Prophylaxis of Human Immunodeficiency Virus Infection After Accidental Exposure

THE POSSIBLE RISK of the transmission of human immunodeficiency virus (HIV) to health care workers following accidental exposure to contaminated blood and body fluids is a prominent concern. Pooled data from ten prospective studies suggest that the incidence of seroconversion after occupational exposure is 0.37%, or less than 1 case of infection per 250 exposures.

Zidovudine is a thymidine analogue that inhibits the viral enzyme reverse transcriptase and also terminates viral-induced DNA synthesis, thus acting as a potent inhibitor of HIV replication. Administering zidovudine has been shown to improve the quality of and prolong life in patients with advanced HIV infection. It delays the destruction of CD4 lymphocytes, the onset of opportunistic infections, and progression to the acquired immunodeficiency syndrome in patients with early and asymptomatic HIV infection. Thus, it appears logical that the early prophylactic administration of zidovudine after accidental HIV exposure might prevent lymphocyte infection and provide an "antidote" for personnel with such exposure. By many criteria, however, zidovudine would be an unlikely agency for postexposure prophylaxis. Zidovudine is an inhibitor of viral replication and functions virostatically by preventing future replication cycles, thus seeming to be best suited to preventing the progression of established infection. Experimental agents exist that prevent HIV entry into lymphocytes—soluble CD4 antigen, dextran sulfate, and heparin—and that selectively destroy HIV-infected cells (GLQ233). These agents may eventually be approved for individual or combined postexposure prophylaxis. Therefore, recommendations made regarding postexposure prophylaxis must be considered dynamic and interim in nature, pending future research.

Only limited studies of zidovudine postexposure prophylaxis have been done in both animals and humans, with inconclusive results. Reports have been published of cases of the failure of zidovudine postexposure prophylaxis after accidental, albeit massive, exposure to HIV. The Burroughs Wellcome Company, makers of zidovudine, has initiated a double-blind, placebo-controlled study of health care workers with such exposure who were given six weeks of zidovudine prophylaxis after the exposure. This study has shown no HIV seroconversion in 84 experimental and control subjects, but the absence of seroconversion in this small group is not surprising.

As data from studies in both animals and humans are currently inadequate, rationales can be made for and against zidovudine postexposure prophylaxis. The rationale for prophylaxis includes the severity and mortality of established HIV infection, the documented antiviral effect of zidovudine in cases of established HIV infection, and preliminary data from studies in animals suggesting a modification of retroviral infection by zidovudine.

The rationale against prophylaxis includes the lack of zidovudine virucidal activity, lack of data showing efficacy in postexposure prophylaxis, limited data on toxicity in uninfected persons, and the carcinogenic properties of zidovudine in rats and mice. Current insight into factors associated with the increased risk of occupational infection is limited, and data collection aimed at exposure and risk stratification, that is, types and route of exposure, body fluid type, volume, age of specimen, stage of illness of donor, and use of zidovudine by donor, is needed. Identifying a type of exposure associated with a higher infection rate (5% to 10%) would advance our knowledge on postexposure risk, define a patient group for therapeutic intervention, and greatly reduce the number of subjects necessary for powerful studies on postexposure prophylaxis.

Models for institutional postexposure programs are more thoroughly described in the accompanying references. If desired, zidovudine therapy should be instituted as soon as possible after exposure, based on data from animals and the knowledge that intracellular HIV infection in CD4 lymphocytes has been established four hours after exposure. The National Institutes of Health use a regimen of 200 mg every four hours (six times a day) for 42 days, and the University of California, San Francisco, General Hospital Medical Center uses 200 mg every four hours (five times a day, skipping the 4 AM dose) for 28 days. Short-term toxicities of zidovudine include marrow suppression—anemia, thrombocytopenia,

granulocytopenia—gastrointestinal symptoms, rashes, constitutional symptoms, and polymyositis. Long-term side effects, such as carcinogenesis and teratogenic effects on future offspring, are unknown. This is of concern because most occupational exposures occur in women of childbearing age.

Future research needs in postexposure prophylaxis include stratifying the risk factors for occupational infection, developing better animal models of HIV infection, designing controlled human studies to determine if zidovudine postexposure prophylaxis or other agents are effective, defining optimal dosing and duration of chemoprophylaxis, determining the long-term toxicity of chemoprophylactic agents, and establishing the duration of follow-up needed to detect HIV infection in workers choosing postexposure prophylaxis.

LOUIS S. BINDER, MD
El Paso, Texas

JAMES A. CHAPPELL, MD
Lubbock, Texas

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Magnesium and Acute Myocardial Infarction

THE ROLE OF MAGNESIUM in cardiovascular disease has received widespread attention. The relationship between hypomagnesemia and arrhythmias has been well documented. Administering intravenous magnesium is now routine treatment in patients with digitalis toxicity who have ventricular arrhythmias and torsades de pointes. Several investigators have also noted the association between magnesium deficiency and coronary artery disease. Magnesium deficiency may even predispose a patient to infarction. An increased risk for thrombosis, increased peripheral vascular resistance, and a promotion of cholesterol deposits have all been associated with a magnesium-deficient state. In the 1950s and 1960s, there were reports of the beneficial effects of magnesium in treating acute myocardial infarction in uncontrolled clinical trials. Since 1984, there have been six randomized, double-blind studies using clinical controlled intervention and one follow-up mortality study of the use of intravenous magnesium in patients with acute myocardial infarctions.

An early study of 76 patients with myocardial infarctions showed that those treated with magnesium infusions needed substantially lower doses of an antiarrhythmic agent than did controls. Of another 130 patients with verified acute myocardial infarction, those randomly assigned to the magnesium infusion group had a 21% incidence of arrhythmias compared with 47% in the placebo group ($P = .003$). A one-year follow-up study of 270 of 273 patients with suspected myocardial infarction showed death from ischemic heart disease occurred in 28% of the placebo group as opposed to 15% in the magnesium-treated group ($P = .006$). Of note, this reduction was almost solely due to a reduction in the mortality within the first 30 days after inclusion in the study. Another study of 185 patients with possible myocardial infarction showed a decrease in mortality and incidence of arrhythmias in the magnesium-treated group. It has also been reported that a single 2.4-gram dose of intravenous magnesium sulfate aborted potentially lethal arrhythmias during the first 24 hours after admission for myocardial infarction in 7 of 48 patients (15%), whereas 16 of 46 patients (35%) receiving placebo had similar arrhythmias ($P = .02$). Another recent report showed patients treated with a continuous infusion of magnesium after a myocardial infarction had significantly fewer episodes of ventricular tachycardia (7 of 25) than did controls (18 of 23) ($P = .0001$). Most recently, in a study of 103 patients, 48 hours of continuous magnesium infusion produced no statistical difference between the incidence of tachyarrhythmias and conduction disturbances in a treated group versus controls. In-hospital mortality figures, 2% (1 patient) in the magnesium-treated group and 17% (9 patients) in the placebo group, were statistically significant ($P < .01$), but death was attributed to hemodynamic factors rather than arrhythmias.

No adverse effects of magnesium infusion have been reported. In all of the noted clinical trials, there was no significant difference in serum magnesium levels between treatment and placebo groups. Thus, the serum value appears to be an inaccurate assessment of the intracellular environment. More accurate results using lymphocyte levels, muscle biopsy concentrations, and magnesium intravenous loading tests have been described.

Postulated mechanisms that continue to gather empiric support and explain the benefits of magnesium infusion in acute myocardial infarction include dilating coronary arteries, inhibiting myocardial calcium overload, preventing arrhythmia, inhibiting platelet aggregation, reducing infarct size, and preventing coronary spasm.

CONNIE MITCHELL, MD
Sacramento, California

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Preventing and Controlling Violence in Emergency Departments

THERE IS WIDESPREAD concern regarding the problem of aggression and violence directed toward staff in hospital emergency departments. Concern over this issue is underscored by a 1987 American Medical Association House of Delegates resolution calling for increased hospital security measures. Until recently, virtually no objective data had been collected about the incidence and magnitude of this problem. The available evidence now suggests that emergency department violence is both widespread and substantial and that many institutions are improperly prepared to deal with it.

A six-month prospective study at the Edinburgh Royal Infirmary accident and emergency department (annual volume, 65,000) showed 102 episodes of violence, half of which involved both verbal abuse and physical assault directed against a staff member. Of all incidents recorded, 37% occurred between 10 PM and 2 AM.

A British National Health Service employee survey found

that 23.2% of accident and emergency department personnel had been threatened with a weapon during the past year, by far the highest incidence of any hospital unit. The study concluded that violence is a serious problem afflicting a wide range of occupations within hospitals, and it emphasized the risk to ambulance staff, nurses, and emergency department personnel.

A one-year retrospective study of emergency department violence at a medium-sized, noncounty, university hospital found that police responded twice a day for patient or visitor aggression directed toward staff. The night shift had 32% of the cases but only 13% of the patient volume. Custody and medical clearance for psychiatry patients accounted for 40% of the total cases.

In a survey of 170 US teaching hospital emergency departments, 43% of respondents reported an episode of physical attack at least once a month, and 18% noted a threatening weapons display at least once a month. A fatal act of violence within the past five years was described by 7%. Many institutions lack 24-hour security personnel, and 40% provide no formal training of nursing staff in recognizing and managing violence. It was recommended that comprehensive risk management guidelines be developed to deal with the possible medicolegal issues of regulating access, the right to search, and failure to restrain versus false imprisonment.

To address violent and aggressive behavior in emergency departments, a multitiered approach is now evolving that encompasses prevention and management. Preventive measures include the control of environmental factors that may provoke those with violent tendencies—such as long waiting times, unpleasant waiting areas, poor patient-family-staff communication—increased security presence, television monitoring, metal detector weapon screening, and training staff to recognize and properly de-escalate aggressive behavior before violence occurs.

Emergency alert systems, personal alarms, panic buttons, and direct telephone lines are among the devices that allow staff to notify security personnel quickly of violent acts. Graded management options include verbal, social, or psychological intervention, show of force, physical restraint, and occasionally pharmacologic tranquilization.

GREGG A. PANE, MD, MPA
Irvine, California

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Neuromuscular Blockage in Emergency Medicine

COMPETENT ACUTE AIRWAY management skills are a necessity for emergency medicine practitioners. Airway management devices designed for ease of placement, such as the esophageal obturator airway, have been shown to be poor replacements for endotracheal tubes. The use of esophageal obturator airways has been discontinued in emergency departments and is becoming increasingly uncommon in the prehospital setting. The emergency department generally does not allow for ideal intubation conditions. Facial trauma, burns, thick secretions, vomitus, immobilization, and combative or intoxicated patients are only some of the factors that can add to the complexity of airway management.

In most cases, emergency airway management can be achieved through the use of topical anesthetics, coupled with intravenous sedation or the use of nasotracheal approaches. The complexity and urgency of the emergency setting demands, however, that physicians be facile in the use of the full range of pharmacologic adjuncts for endotracheal intubation. This includes the use of neuromuscular blocking agents. A number of recent studies have shown that these agents can be used safely in emergency departments. They are particularly helpful in achieving successful airway management in patients with acute trauma or poisoning.

Of the neuromuscular blocking agents currently available, emergency physicians are most familiar with succinylcholine chloride and pancuronium bromide. Succinylcholine is a depolarizing neuromuscular blocking agent used in a dose of 1 to 1.5 mg per kg by intravenous push. It provides excellent muscle relaxation for intubation within 60 seconds and lasts 3 to 5 minutes. These kinetics make it a nearly ideal agent for urgent airway intubations, and it has been shown safe for emergency intraosseous administration. Its use can sometimes be associated with side effects including bradycardia, hypotension, increased intracranial pressure, and, rarely, hyperkalemia. Nonetheless, succinylcholine is the current agent of choice in most emergency departments.

Pancuronium bromide is a nondepolarizing neuromuscular blocking agent that is not associated with most of the potential complications of succinylcholine. Pancuronium has, however, a relatively slow onset of action, as long as 5 minutes, and produces a long paralysis lasting as long as 45 to 60 minutes. These factors do not make it an ideal agent for emergency intubation.

Two newer, intermediate-acting neuromuscular blocking agents, atracurium besylate and vecuronium bromide, provide alternatives. These agents are nondepolarizing neuromuscular blocking agents and therefore are not complicated by the side effects seen with succinylcholine use. Their onset of action for intubation is about 2 minutes, and their duration of action is 20 to 30 minutes. Vecuronium is given as a dose of 0.1 to 0.15 mg per kg, requires reconstitution, and can have an extended half-life in patients with underlying liver disease. Atracurium is given as a dose of 0.4 to 0.5 mg per kg and requires refrigerated storage. Neither atracurium nor vecuronium causes appreciable hemodynamic change or histamine release, particularly when given over one minute.

The potential for the misuse of neuromuscular blocking agents in the emergency department must be seriously considered. An area of great concern is that a sizable percentage of both medical and nursing staffs fail to recognize that neuromuscular blocking agents have absolutely no analgesic or anxiolytic properties. The fact that patients are physically unable to respond to pain is sometimes interpreted as an inability to consciously experience pain. This generally is not a problem at the time of initial intubation but rather when neuromuscular blockage is continued for other purposes. In such cases, it is imperative that patients be provided with analgesic or sedative medications. If there is concern about the need to assess mental status after a neuromuscular blocking agent has worn off, then the use of narcotic medications may be preferable because of their ability to be immediately

reversed with naloxone hydrochloride. The use of neuromuscular blocking agents should be avoided in patients who are spontaneously breathing but who might be particularly difficult to either intubate or ventilate after paralysis, such as patients with severe asthma, facial or laryngeal trauma, or supraglottitis. When the above-described cautions and contraindications are observed, neuromuscular blocking agents provide a highly useful and sometimes necessary role in aiding acute airway management.

EDWARD A. PANACEK, MD
Cleveland, Ohio

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Transvaginal Imaging of Ectopic Pregnancy

ADVANCES IN TRANSDUCER TECHNOLOGY have now produced transvaginal ultrasound imaging. A transvaginal probe is inserted into the vagina, providing an "unobstructed" view of the pelvic organs. The higher resolution transducers produce images of remarkable clarity, and the accuracy for defining an ectopic pregnancy is greater than with the transabdominal technique. Whereas previous reports have suggested a sensitivity on the order of 70% to 80% with transabdominal study, the sensitivity of the transvaginal technique is 95% to 100%.

The diagnosis of an ectopic pregnancy is virtually eliminated by defining an early intrauterine gestation. When the pregnancy is intrauterine, a 4½- to 5-week gestation may be diagnosed with relative certainty with transvaginal imaging. Similarly, the transvaginal ultrasonographic evaluation can define a living ectopic pregnancy at an early gestational age. Transvaginal imaging may show blood or solid irregular material, possibly a hematoma.

With the improved resolution offered by the transvaginal technique, the percentage of unruptured ectopic pregnancies discovered should increase. By adding color Doppler evaluation, the increased blood flow associated with ectopic pregnancies can be seen. In addition, identifying a "corpus luteum" by Doppler findings will also help locate the site of a pregnancy. These techniques should lead to early therapy and the sparing of Fallopian tubes.

There are many pitfalls in ultrasound imaging. The technique can be difficult, especially for the transvaginal examination. An ectopic pregnancy may, in fact, be out of the field of the transvaginal image so that a full transabdominal study would be required.

In summary, the transvaginal pelvic examination aids in the ability to diagnose ectopic or early intrauterine pregnancy or to suggest the absence of disease. Care must be taken not to overshadow clinical considerations. On the horizon are improved resolution and color Doppler capabilities. Transvaginal ultrasonography should be used routinely.

MICHAEL CRADE, MD
Long Beach, California

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Rectal Diazepam Therapy for Prehospital Pediatric Status Epilepticus

SEIZURES ARE A COMMON pediatric prehospital emergency. Of 889 consecutive patients younger than 18 years requiring prehospital advanced life support and monitored by the San Francisco General Hospital Medical Center over a 12-month period, 1989 to 1990, seizures constituted 34% of medical complaints. Other epidemiologic data on prehospital pediatric care have similarly shown that seizures are the commonest childhood condition confronting emergency medical technicians. Most convulsive episodes in children, however, are brief and do not require treatment. A small number progress to status epilepticus, defined by continuous or repeated convulsions without an intervening return of consciousness for at least 15 minutes. These patients often present vexing field management problems, especially because of difficulties in establishing vascular access and the high incidence of respiratory depression due to rapid intravenous diazepam administration.

Recent studies have shown a varying correlation between the duration of status epilepticus and neurologic outcome. Morbidity appears to be most correlated with cause, even for status epilepticus lasting more than an hour, except in very young patients with severe underlying disease, such as meningitis, prolonged submersion, or hypoglycemia. Therefore, a safe, slow-acting, first-line anticonvulsant agent with a high therapeutic ratio is needed. One such agent is rectal diazepam, which has been used safely and effectively in the home and hospital but has not been widely used in the field.

The preferred agent is undiluted intravenous diazepam solution. The drug is lipid soluble and is promptly absorbed from the highly vascularized rectal mucosa through the superior, middle, and inferior hemorrhoidal veins. Therapeutic serum concentrations are present in 5 to 10 minutes. The time to peak concentration varies, ranging from 5 to 60 minutes, but typically serum drug peaks occur in 10 to 20 minutes after rectal administration.

Rectal diazepam therapy will obliterate status epilepticus in more than 80% of cases. Seizures longer than 15 minutes may be less amenable to treatment by this method. The only study of prehospital rectal diazepam use for pediatric status epilepticus confirmed a high rate of efficacy (82%), using 0.3 to 0.5 mg per kg of parenteral diazepam solution per high rectal tube, in 11 children. Two patients who did not respond to rectal diazepam required extensive emergency department treatment, including the use of multiple anticonvulsants and endotracheal intubation. Both had encephalitis. No treated patient whose seizures stopped had a serious complication. Other studies of rectal diazepam use have shown an incidence of systemic complications of less than 1%. The most common complication is respiratory depression. Emergency medical technicians using parenteral or rectal diazepam in the field must be capable of providing airway and breathing support.

The method of rectal diazepam administration is simple. First, calculate the dose of diazepam (0.3 to 0.5 mg per kg) based on estimated body weight (maximum dose 10 mg). Draw the intravenous diazepam solution into a disposable tuberculin syringe and discard needle. Alternatively, draw the diazepam into a 3-ml syringe with attached blunt-tipped #5 French pediatric feeding tube. Next, insert the lubricated tuberculin syringe or flexible feeding tube 5 cm into the

rectum and inject the solution. Clear the tubing with 1 ml of air. Tape buttocks closed. Repeat dose in five minutes if the seizure continues.

The rectal route eliminates the need for intravascular access. This is particularly advantageous in children with status epilepticus, where immediate venous access is difficult.

RONALD A. DIECKMANN, MD
San Francisco, California

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Bacterial Meningitis in Emergency Departments

DESPITE OUR GROWING UNDERSTANDING of the pathogenesis of bacterial meningitis and an enlarged spectrum of antibacteriologic agents, bacterial meningitis remains an important cause of morbidity and mortality in the United States. More than 80% of cases of bacterial meningitis are caused by one of three organisms, *Hemophilus influenzae* (45%), *Neisseria meningitidis* (25%), and *Streptococcus pneumoniae* (10%), with United States mortality rates from 1978 to 1981 of 6.0%, 10.3%, and 26.3%, respectively.

Bacterial meningitis is a medical emergency, and a delay in administering antibiotics may be harmful. Unfortunately, there are frequent delays in therapy. Recently 122 cases were reviewed, and a median time delay in administering antibiotics of 3.0 hours was found, in contrast to the accepted "gold standard" of less than 30 minutes. Of note, 90% of the total time to antibiotic administration occurred after the initial physician encounter, often as a result of awaiting computed tomography or laboratory results. This delay is largely avoidable, and a review has been published addressing early antibiotic therapy and the issue of jeopardizing the diagnosis based on cerebrospinal fluid findings. Several studies have assessed interval cerebrospinal fluid analysis during intravenous antibiotic therapy. All, however, address intervals of 24 to 48 hours and not the 2 to 3 hours that might be expected in an emergency department. Although culture results might be affected by antibiotic administration in the emergency department, cerebrospinal fluid leukocyte counts and glucose and protein values are much less affected. Thus, the diagnosis of meningitis would not be obscured by an early initial dose of the appropriate antibiotic, and common sense suggests that the sooner the antibiotics are given, the better the outcome for the patient.

Mediators of inflammation, specifically interleukin-1 and tumor necrosis factor, have been recently implicated in the pathophysiology of bacterial meningitis. After colonizing the nasopharynx, the invading agent gains access first to systemic circulation and then to the cerebrospinal fluid, probably through the choroid plexus, producing subarachnoid space inflammation and local vasculitis. Cerebral vasospasm or cortical thrombophlebitis may explain the seizures or focal neurologic deficits often seen with bacterial meningitis. Efforts to modify this process using anti-inflammatory agents have shown promise. A double-blind placebo-controlled study of the use of dexamethasone (0.15 mg per kg every six hours for four days) was done on 200 infants and children, and a statistically significant decrease was found in the incidence of hearing loss (15.5% to 3.3%) in those patients receiving steroids. Another study using an open, prospective, randomized design evaluated the use of dexamethasone (without placebo control) in 429 patients with bacterial meningitis, and an overall decrease in the case-fatality rate and a decrease in adult hearing loss after pneumococcal meningitis were found. Although these findings are promising, firm recommendations regarding steroid use in adult patients or for children not suffering from *H influenzae* meningitis await further prospective, controlled clinical trials.

After treatment is initiated, contact chemoprophylaxis must be considered because selected close contacts have a 200 to 1,000 times risk rate compared with the general population. Close contacts of all ages are at risk of meningococcal meningitis, whereas the vulnerability of *H influenzae* meningitis contact is limited primarily to young children. Studies of household contacts of patients with *H influenzae* infection have found a 4.0% incidence of secondary disease in children younger than 2 years, 2.0% for children aged 2 to 3, and 0.1% for children aged 4 to 5. To highlight the low risk to health professionals, the Centers for Disease Control describe contacts at risk as "intimate contacts," defining them as household members, day-care-center contacts, and anyone with direct exposure to a patient's oral secretions, such as through mouth-to-mouth resuscitation or kissing. By contrast, prophylaxis is not indicated for persons who have had casual contact at either workplace or a classroom nor for most hospital personnel. In addition, because of the influence of age on secondary *H influenzae* disease, prophylaxis is recommended only for groups who have as one of their members a child younger than 4 years. Even so, as the effectiveness of chemoprophylaxis cannot be entirely relied on, close follow-up of those at risk may be the most important intervention. Rifampin remains the drug of choice for eliminating pharyngeal carriage of both *H influenzae* and the meningococcus. Because pharyngeal colonization may persist after traditional intravenous therapy, the treated index patient must also receive rifampin therapy before hospital discharge. The current recommendations for rifampin chemoprophylaxis are, for meningococcal disease, 600 mg orally every 12 hours for 2 days for adults, or 10 mg per kg (maximum of 600 mg) orally every 12 hours for 2 days for those aged 1 month to 12 years. For *H influenzae* disease, the recommendation for adults is 600 mg orally every 24 hours for 4 days and for those aged 1 month to 12 years is 20 mg per kg (maximum 600 mg) every 24 hours for 4 days. Recent work with ciprofloxacin and ceftriaxone sodium shows promise for simple and effective meningococcal prophylaxis, but changes in the Centers for Disease Control recommendations await further clinical trials.

ERIC WEISS, MD
Woodside, California

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Human Immunodeficiency Virus Precautions in Emergency Departments

PREVENTING EXPOSURE to the human immunodeficiency virus (HIV) and other blood-borne pathogens is important in emergency departments. Recent studies have shown low compliance rates with barrier precautions recommended by the Centers for Disease Control. It has been suggested that improvements in design of intravenous catheters and phlebotomy equipment could reduce the incidence of needle-stick injuries. Although the seroprevalence rates for HIV and hepatitis vary among institutions, all bodily fluids in all patients should be considered potentially infectious in the emergency setting.

The major risk to emergency personnel is needle sticks. Recently developed intravenous catheters now provide an integrated plastic sheath that covers the needle stylet after insertion of the catheter. For patients requiring phlebotomy after catheter insertion, vacuum tube assemblies are available that can be inserted directly into the intravenous catheter. These assemblies fill laboratory tubes directly and do not require the transfer of blood from syringes through needles.

Needle-stick injuries may also occur when needles are inserted into intravenous tubing—"piggybacking." New devices provide a needle and sheath assembly that prevents needle-stick injuries in these cases. These devices also include a locking mechanism that prevents accidental dislodgement of the needle from the intravenous tubing.

The use of winged-needle intravenous catheters, or "butterflies," should be avoided whenever possible. The disposal of these devices, as well as their removal from laboratory tubes, has resulted in a relatively high rate of needle-stick exposures.

If a needle and syringe assembly must be used for a phlebotomy, then a two-handed technique of holding the syringe in one hand and holding blood tubes in the other should never be used. Test-tube racks should hold laboratory tubes, and one hand should be used to fill the upright laboratory tubes.

Needles should not be recapped. If immediate disposal is not possible, however, and recapping is necessary, a one-handed technique should always be used. Never hold the cap of a needle in one hand while inserting a needle into the cap with the other. Rather, the cap should be scooped up with the needle while the cap is lying on a flat surface. Convenient plastic receptacles should be placed at the bedsides of all patients for use by health care workers who do intravenous insertions and phlebotomies. These receptacles must be replaced frequently to avoid needle sticks due to overfilled boxes.

Skin and mucous membrane exposure is further prevented by using gloves, masks, protective eyewear, and gowns. These items must be easy to reach and easy to use for all health care personnel, especially in areas where invasive procedures are done or where trauma or cardiac arrest patients are resuscitated. Barrier protection should also be readily available to health care personnel irrigating wounds. Umbrellalike devices that fit onto irrigation instruments are now available and prevent the backsplash associated with high-pressure irrigation devices. Gloves should be worn whenever skin may become contaminated with blood.

New personnel must be trained and compliance with infection control protocols monitored in every emergency department. Postexposure counseling and testing of source patients and exposed medical staff must be provided. Counseling should include a discussion of confidentiality issues, the frequency of testing, and the use of hepatitis immune globulin and zidovudine (AZT).

ALAN GELB, MD
San Francisco, California

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High-Dose Epinephrine in Cardiac Arrest

EPINEPHRINE IS ONE of the few drugs with proven efficacy in cardiac arrest, but its optimal dose is unknown. Epinephrine achieves its beneficial effects by α-adrenergic vasoconstriction of the peripheral circulation, thereby increasing blood flow through the heart and brain. This was demonstrated in animals in the early 1960s, laying the groundwork for advanced cardiac life support (ACLS) standards. These studies, however, used doses of 100 μg per kg or more, whereas ACLS standards recommend only 7.5 to 15 μg per kg in humans (0.5 to 1 mg in an adult). There was no further comment or study of this discrepancy during the following decade.

A series of careful studies in animals in the 1980s rekindled interest in the optimal dose. Doses of 20 μg per kg were shown not to provide the necessary coronary artery perfusion to resume spontaneous circulation. Doses of 200 μg per kg comfortably met this goal and often produced blood flow approaching normal, nonarrested levels. Case reports of humans suggested that larger doses of epinephrine could cause a return of perfusing rhythm, even in patients with long arrest times and unfavorable cardiac rhythms, but most died of brain damage within 24 hours. Case series of patients with prolonged cardiac arrest have shown that epinephrine doses of 200 μg per kg can substantially raise diastolic blood pressure and coronary artery perfusion pressure, often doubling the latter and achieving levels greater than those needed to resume spontaneous circulation. Standard ACLS doses do not achieve this.

High doses of epinephrine of 200 μg per kg caused at least a brief return of spontaneous circulation in 60% of adults with prolonged cardiac arrest versus 15% who received a standard dose of 15 μg per kg. Therapy was not randomized, however. Children in arrest in whom initial standard ACLS therapy failed and who were then randomly selected for either continued standard doses or high doses of epinephrine were never resuscitated with standard doses. High-dose epinephrine resuscitated 70%, however, and 40% survived. Only 38% of survivors were neurologically intact, but high rates of poor neurologic outcome are typical of children with cardiac arrest. Most recently, 68 patients who were resuscitated from cardiac arrest and who received varying doses of epinephrine at the discretion of the clinician were examined to determine if there was any difference in various cardiovascular, pulmonary, endocrine, neurologic, and other complication rates between those receiving high doses and those

receiving standard doses of epinephrine. Despite the fact that the average patient given high-dose epinephrine received 20 mg and some received more than 100 mg of epinephrine, none of these complications were detected.

Several prospective blind clinical trials of the use of high-dose epinephrine in prehospital cardiac arrest are currently under way, but results are not yet available. No definitive recommendation can be made as to which dose clinicians should use. The ACLS standards continue to recommend 7.5 to 15 μg per kg. Clinicians who use these doses are following official ACLS guidelines but may be failing to resuscitate some patients whose lives could be saved. On the other hand, using high-dose epinephrine may eventually prove to be of no long-term benefit. Indeed, it may resuscitate more patients who require intensive care unit resources for a few days before they die of neurologic complications.

MICHAEL CALLAHAM, MD
San Francisco, California

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When to Image Cervical Spine Injuries

MOST PROTOCOLS for the emergency evaluation of patients with multiple trauma call for a liberal use of cervical spine x-ray films because of the fear that failing to diagnose occult injuries could lead to catastrophic consequences. This approach has been challenged because it leads to taking a great many films for each one that identifies an injury requiring specific treatment and because asymptomatic cervical spine injury may not exist: most published cases of purported asymptomatic injury have elements that suggest that they were occult rather than truly asymptomatic. In addition, a number of studies have identified "low-risk criteria" that should essentially exclude important cervical spine injury in certain patients.

Before attempting to selectively limit cervical spine films in patients with many injuries, it is crucial to exclude patients in whom there is a clinical suspicion of cervical spine injury, for whatever reason. These include patients with underlying bone diseases that predispose them to fractures, such as diffuse ankylosing spondylitis or severe osteoporosis, and patients with high-risk mechanisms of injury, such as high-speed motorcycle accidents or dives into an empty pool. In all other patients with a potentially serious mechanism of injury, cervical spine radiography is appropriate unless all of the following criteria are met: the patient does not have neck pain, the patient does not have tenderness to direct palpation over bony spinous elements, the patient has no focal neurologic deficits, the patient is awake and normally responsive, the patient shows no evidence of intoxication with alcohol or other drugs, and the patient does not have a substantially painful injury that might alter pain perception or distract attention away from a possible cervical injury.

X-ray films of the cervical spine are critical for patients with major multiple trauma, who have signs or symptoms suggesting cervical spine injury, or other conditions that can be expected to interfere with the adequacy of clinical evaluation, such as altered mentation from head injury or intoxication, or other severely painful injuries that could distract a patient's attention. They are not helpful, however, in the evaluation of awake, alert, sober, neurologically intact persons who are asymptomatic or have only mild discomfort limited to the paraspinous muscles and soft tissues. Limiting cervical spine radiographs according to these criteria would decrease by perhaps 30% to 50% the number of films taken, with virtually no risk that clinically important injuries will be missed.

JEROME R. HOFFMAN, MD
WILLIAM MOWER, MD
Los Angeles, California

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Terminating Paroxysmal Supraventricular Tachycardias With Adenosine

THE EFFECTS OF adenosine preparations on atrioventricular (AV) node conduction were noted as early as 1929. In the 1980s, research on adenosine accelerated, and in 1989 it was approved for the termination of acute paroxysmal supraventricular tachycardia. Adenosine is an endogenous purine nucleoside with receptors in many tissues. The mechanisms of adenosine's effects on cardiac tissue are not fully understood but appear to involve the modulation of adenylate cyclase activity and direct effects on potassium channels. Relevant clinical effects include transient depression of sinoatrial node automaticity and AV node conduction. It produces brief periods of bradycardia and will terminate most reentrant supraventricular tachycardia involving the AV node.

The efficacy of adenosine use has been studied in both the clinical setting and electrophysiology laboratories. It terminates between 90% and 95% of episodes of paroxysmal supraventricular tachycardia due to AV node reentry or AV tachycardia using an accessory pathway. Although other atrial tachycardias may not terminate, slowed conduction through the AV node may reveal an underlying atrial fibrillation or flutter rhythm. Several studies have shown that although adenosine does not terminate most ventricular tachycardias, it can be safely given to patients with hemodynamically stable, wide-complex tachycardia of uncertain origin. Termination strongly suggests an AV node reentrant mechanism. Other atrial tachycardias may be slowed enough for diagnosis of the atrial pattern, and ventricular tachycardia will usually be refractory. Occasional conversion of ventricular tachycardia that is caused by catechol-dependent mechanisms has been reported.

Adenosine is given intravenously as a rapid bolus, preferably into a large vein, followed by a fluid flush. Much of a dose may be inactivated before reaching the heart if given in a small peripheral vein. Patients who do not have response to the initial dose of 6 mg or who revert to supraventricular tachycardia shortly after conversion (approximately 30% may do so) may receive a second dose of 12 mg after one to

two minutes. A third dose of 12 mg may be given if the arrhythmia has not broken or recurs. Adenosine has been used safely in children. Recommended doses are 37.5 μg per kg repeated to a maximum of 350 μg per kg. One of the benefits of adenosine rests in its rapid metabolism within the vascular system. Following an intravenous bolus, the estimated half-life is less than 10 seconds, and total clearance occurs within 30 seconds. This translates to a rapid onset of action and a short duration for desired and undesired clinical effects.

Reported side effects include facial flushing (18%), shortness of breath (12%), chest pressure (7%), and lightheadedness or nausea (2% to 3%). Effects reported in less than 1% include palpitations, hypotension, dizziness, numbness, and occasional pressure sensations. These effects are common but usually last less than a minute. If a patient is advised of them beforehand, they are usually well tolerated. Following the intravenous bolus, the monitor may show a brief sinus pause or bradycardia with extrasystoles or short runs of tachycardia. Persistent asystole, ventricular tachycardia, or ventricular fibrillation has not been reported. There is a theoretic risk of hemodynamic collapse due to shortening of the atrial or accessory pathway refractory period followed by rapid atrial fibrillation.

Contraindications include the sick-sinus syndrome and second- or third-degree AV block, unless a functioning pacemaker is in place. Caution is advised in patients with a history of asthma or wheezing. Inhaled adenosine causes bronchospasm in patients with asthma, and experience is limited in these patients. Adenosine should not be used when a patient's clinical state requires immediate cardioversion. It has, however, been safely and successfully used in patients on concomitant β-blocker therapy and in patients with hypotension—systolic blood pressures as low as 80 mm of mercury—or congestive heart failure. Drug interactions include antagonism by methylxanthines and potentiation by dipyridamole. Dosing adjustments for patients taking these drugs are not yet available.

In summary, adenosine is a safe and effective drug for terminating supraventricular tachycardia. It compares favorably with verapamil in terms of efficiency, although it is more costly. It carries less risk of hypotension or deterioration to a more ominous rhythm. It may be used as a diagnostic tool in wide-complex tachycardia of presumed supraventricular origin and may occasionally convert triggered ventricular tachycardia. Emergency medical experience with adenosine is increasing, and trials are ongoing in the prehospital setting.

JULIA NATHAN, MD
San Francisco, California

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State Chapter of California, Inc
Woodland Hills

Alerts, Notices, and Case Reports

Severe Thyrotoxicosis Presenting as Acute Psychosis

TIMOTHY G. CAUDILL, MD
CLAUDE K. LARDINOIS, MD
Reno, Nevada

ACCIDENTAL EXPOSURE to thyroid hormone products is common.[1-4] The American Association of Poison Control Centers Collection System reported more than 2,200 exposures to thyroid hormone products in 1986.[5] Classic symptoms of thyrotoxicosis include nervousness, hyperhidrosis, palpitations, fatigue, weight loss, and a fine resting tremor. The psychiatric symptoms may vary from a delirious state to one of hyperexcitability simulating mania. We report the case of a teenaged girl with acute psychosis after probable but unintentional exogenous thyroid ingestion.

Report of a Case

The patient, a 16-year-old adolescent girl, was admitted to the hospital because of severe headaches, confusion, and bizarre behavior for two days. She had been well before the symptoms began, when she was noted to become increasingly more confused and withdrawn, dressing inappropriately, and having bizarre speech. There had been no history of exposure to unusual illness or of drug abuse. Of significance was a medical history of depression, an episode of "hysterical" blindness, and suicidal behavior on at least two previous occasions. She was sexually active and fearful she might be pregnant. She had not had psychiatric treatment. The family history was significant for a sister who was sexually molested by a friend of her stepfather. Another sister was reportedly raped, and the stress associated with this forced the family to move from a small town in Oregon. Her younger brother was also taking several illicit drugs. She was brought by her parents to the emergency department where she was noted to be extremely agitated and uncooperative, necessitating the administration of 100 mg of chlorpromazine hydrochloride (Thorazine).

On physical examination her pulse rate was 112 beats per minute, and her blood pressure and temperature were normal. The findings of a neurologic examination were entirely normal, and her toes were downgoing bilaterally. Of note was the absence of a thyroid goiter, resting tremor, or hyperreflexia.

Initial laboratory studies revealed a normal complete blood count and chemistry profile except for a cholesterol level of 2.25 mmol per liter (87 mg per dl). A drug screen for major substances of abuse was negative. A serum thyroxine level was markedly elevated at 1,193 nmol per liter (normal, 50 to 154), and the thyroid-stimulating hormone (TSH) level was below the level of sensitivity in the ultrasensitive assay, strongly suggesting thyrotoxicosis. The free thyroxine level was 97 pmol per liter (normal 10 to 29), and a triiodothyronine value was 25.8 nmol per liter (normal 1.2 to 3.4). Thyroglobulin was undetectable, and a scan using technetium Tc 99m pyrophosphate showed no demonstrable thyroid uptake over a 30-minute period. An electrocardiogram showed sinus tachycardia with occasional premature ventricular contractions. An electroencephalogram showed diffuse activity suggestive of a hypermetabolic state.

On admission to the hospital, she was extremely agitated and thrashed around in bed, requiring four-point restraints. She yelled, screamed, bit herself, and showed paranoid behavior. She was confused and disoriented to person, place, and time. Treatment with propranolol hydrochloride (Inderal), 40 mg every four to six hours; dexamethasone (Decadron), 2 mg every six hours; and chlorpromazine, 50 mg every four hours, was instituted. Over the next few days she remained confused, frequently wandered into other rooms, and on several occasions thought she saw her mother sitting in a chair. Additional drug therapy included haloperidol (Haldol) decanoate, thioridazine hydrochloride (Mellaril), and thiothixene hydrochloride (Navane). Over the next several days, she became more alert, less agitated, and oriented to her surroundings. All antipsychotic drugs were discontinued three days before discharge. The results of serial thyroid function tests were monitored closely, as shown in Figure 1.

Further questioning of the patient regarding the ingestion of exogenous thyroid hormone revealed no intentional ingestion. None of her immediate family had been taking any thyroid preparations. She had not eaten any hamburger made from neck tissues that might have included beef thyroid. A question of accidental ingestion was raised when she admitted being at a party three days before the onset of her symptoms. The delay in biotransformation of thyroxine to triiodothyronine suggests that the ingestion occurred more than 24 hours previously.

Discussion

There are many causes of thyrotoxicosis that a clinican must consider in dealing with a case such as this.[6] The more common causes include Graves' disease, toxic adenoma, toxic multinodular goiter, choriocarcinoma, hydatidiform

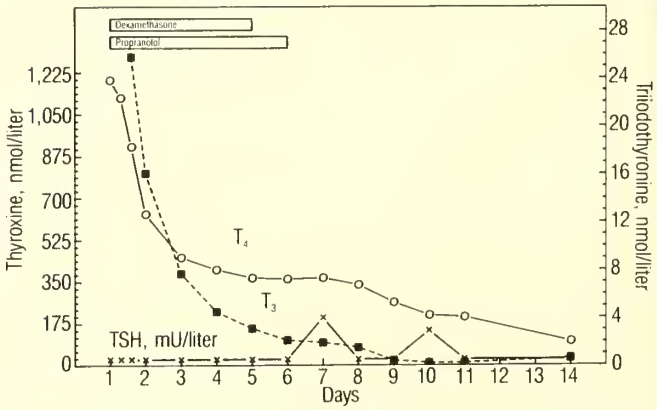

Figure 1.—Serial changes are shown in thyroxine (T_4), triiodothyronine (T_3), and thyroid-stimulating hormone (TSH) concentrations after the administration of dexamethasone and propranolol hydrochloride.

(Caudill TG, Lardinois CK: Severe thyrotoxicosis presenting as acute psychosis. West J Med 1991 Sep; 155:292-293)

From the Department of Medicine (Drs Caudill and Lardinois), Division of Physiology (Dr Lardinois), University of Nevada School of Medicine, and the Department of Medicine, Division of Endocrinology, Veterans Affairs Medical Center (Dr Lardinois), Reno, Nevada

Reprint requests to Claude K. Lardinois, MD, Department of Medicine (111), VA Medical Center, 1000 Locust St, Reno, NV 89520.

mole, TSH-secreting pituitary tumor, iodine-induced hyperthyroidism, thyroiditis, and exogenous hormone ingestion. The key test to do to sort out the causes of thyrotoxicosis is the radioiodine uptake of the thyroid gland. A normal or increased uptake ensures that the gland is the source of the thyrotoxicosis, and a low uptake means that the source of the excess thyroid hormone is outside the thyroid gland or that the gland is injured.

In the case reported here, the young woman had greatly elevated thyroid hormone levels but, except for the severe agitation and tachycardia, did not show the classic constellation of symptoms suggestive of thyrotoxicosis. Her low thyroid uptake narrowed the differential diagnosis down to exogenous hormone ingestion (thyrotoxicosis factitia) and thyroiditis. Clinicians may differentiate between these two causes of thyrotoxicosis by evaluating a patient's thyroglobulin levels. Thyroglobulin is the thyroid hormone containing protein that is stored in the colloid within the thyroid follicles. During acute inflammation of the thyroid gland, as with thyroiditis, thyroglobulin is released into the serum along with thyroxine and triiodothyronine, resulting in an elevated serum thyroglobulin level. This is not true of exogenous thyroid administration, however, where the thyroglobulin levels are generally undetectable.[7] The finding of a low thyroglobulin level in our patient excludes the possibility of thyroiditis and strongly suggests the ingestion of exogenous thyroid hormone. Initially it was thought that she might be suffering from euthyroid hyperthyroxinemia of acute psychosis. As many as 30% of patients presenting with acute psychiatric illnesses may have findings consistent with thyrotoxicosis that are indistinguishable from other causes.[8] The notably elevated values of her thyroid function tests, however, made this diagnosis unlikely.

Current therapy for thyrotoxicosis includes decreasing the thyroid hormone production by the thyroid gland, blocking thyroid hormone release, and reducing the peripheral action of thyroid hormone. In this particular case, the patient responded to a combination of propranolol and dexamethasone. Both of these agents act to decrease the peripheral conversion of thyroxine to the more biologically active triiodothyronine. Propranolol also has the added benefit of blocking the adrenergic effects of the elevated thyroid hormone levels on peripheral tissues such as the myocardium. To our knowledge, this is the first reported case using dexamethasone therapy for thyrotoxicosis factitia. Its use in thyroid storm is well described and is applicable to exogenous thyroid hormone ingestion as well.

The acute ingestion of thyroid hormone may not present with the "classic" symptoms of thyrotoxicosis, as illustrated by the case reported here. Clinicians must use their intuition to include thyroid function testing as part of the differential diagnosis when patients present with acute psychosis.

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Cardiomyopathy Associated With High-Dose Interleukin-2 Therapy

ANNA C. BECK, MD
JOHN H. WARD, MD
ELIZABETH H. HAMMOND, MD
ROBERT B. WRAY, MD
WOLFRAM E. SAMLOWSKI, MD
Salt Lake City, Utah

RECOMBINANT INTERLEUKIN (IL)-2 is active as an antineoplastic agent in the treatment of disseminated renal cell cancer and melanoma.[1,2] Treatment with high-dose IL-2 (600,000 IU per kg every eight hours by intravenous bolus) has led to a 20% to 30% response rate, including 8% to 12% complete remissions.[3] Unfortunately, high-dose IL-2 therapy has been associated with serious cardiovascular side effects.[4-8]

A dose-dependent increase in vascular permeability, termed the "vascular leak syndrome," develops in all patients.[2] This is accompanied by decreases in intravascular volume and systemic vascular resistance, resulting in hypotension and tachycardia.[4-8] Fluid, colloid, or vasopressor support is usually required to maintain adequate tissue perfusion.[1,6] Pulmonary artery catheterization studies have shown that cardiac output and work increase during IL-2 administration.[4,7] This "high-output" state may exacerbate underlying ischemic heart disease.[1,4-6]

Transient myocardial dysfunction has been recorded during IL-2 therapy.[4,7,8] The cardiac ejection fraction is frequently depressed during IL-2 therapy, despite increased heart rate and decreased systemic vascular resistance. This alteration in cardiac performance is reversible over time. These findings are similar to the cardiovascular manifestations of septic shock, suggesting a related pathophysiology.[9] Irreversible heart damage following IL-2 administration is unusual. We report the case of a patient in whom acute cardiomyopathy developed after high-dose IL-2 therapy and who eventually died of probable persistent myocardial damage.

Report of a Case

The patient, a 50-year-old woman, saw her physician for the evaluation of an enlarging left buttock mass in January 1989. An excisional biopsy of the mass revealed a poorly differentiated tumor with ultrastructural features suggestive of malignant melanoma. Staging evaluation detected a left

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From the Department of Internal Medicine (Drs Beck, Ward, Wray, and Samlowski), University of Utah-Veterans Affairs Medical Center Cancer Immunotherapy Program (Drs Ward and Samlowksi), and the Department of Pathology (Dr Hammond), University of Utah School of Medicine; the Department of Pathology, LDS Hospital (Dr Hammond), and the Department of Veterans Affairs Medical Center (Dr Samlowski), Salt Lake City.

Reprint requests to Wolfram Samlowski, MD, Division of Hematology/Oncology, 4c 416 University of Utah Medical Center, Salt Lake City, UT 84132.

ABBREVIATIONS USED IN TEXT

FEV_1 = forced expiratory volume in 1 second
FVC = forced vital capacity
IL = interleukin

upper quadrant mass, a nodule at the base of her right lung, and invasion of metastatic melanoma into the small bowel. All tumor in the abdomen was resected. After the operation, she received chemotherapy with dacarbazine until a new pancreatic mass developed in June 1989. She was then referred to the University of Utah Medical Center for high-dose IL-2 and lymphokine-activated killer cell therapy.

She had no history of any serious medical disorder. She had never used tobacco or alcohol.

On physical examination, her heart was normal, without murmurs or gallops. There was mild diffuse tenderness of the abdomen. A laboratory evaluation revealed a normal complete blood and differential cell count. A screening chemistry panel elicited only a minimally elevated γ-glutamyl transpeptidase level. A chest radiograph showed a normal cardiac silhouette with a circumscribed nodule in the right lower lobe. On computed tomography there was a right lower lobe parenchymal nodule, abdominal lymphadenopathy, and a soft tissue density of the left gluteal muscle. Pulmonary function studies gave a forced expiratory volume in one second (FEV_1) of 3.85 liters, a forced vital capacity (FVC) of 4.5 liters, and a normal FEV_1:FVC ratio of 85.6%. An electrocardiogram was normal. She had a normal left ventricular ejection fraction (0.57) with normal wall motion on a multiple-uptake gated acquisition cardiac scan and normal myocardial perfusion during rest and exercise on a stress thallium scan.

The patient met previously published eligibility criteria[2,6] and was admitted for her "priming" course of IL-2 in August 1989. She felt well on admission. Therapy was instituted with 47.2×10^6 IU of IL-2 (600,000 IU per kg; Cetus Corporation, Emeryville, California) every eight hours by intravenous bolus for five days.[2] Concomitant oral medications included acetaminophen, 650 mg every four hours, and indomethacin, 25 mg every eight hours. Meperidine hydrochloride, 25 to 50 mg intravenously, was used as needed to diminish chilling and fevers associated with IL-2 administration. Ranitidine, 150 mg orally twice a day, and an oral sucralfate slurry, 1 gram by mouth every six hours, were administered to prevent gastrointestinal bleeding and mucositis, respectively.

Expected side effects developed that consisted of generalized malaise, anorexia, and mild pruritus. Oliguria (<250 ml of urine per eight hours) required treatment with fluids and dopamine, 2 to 5 mg per kg per minute. Blood pressure was maintained at above 90/50 mm of mercury. The patient tolerated all 14 scheduled doses of IL-2 in the priming course. By the time the IL-2 course was completed, her weight had increased by 5.2 kg, and on physical examination she had bibasilar rales without abnormal heart sounds or peripheral edema. A chest radiograph showed bilateral pleural effusions, peribronchial cuffing, and a normal cardiac silhouette. Despite continued treatment with dopamine, diuretics, and infusions of salt-poor albumin, oliguria persisted. She was transferred to the medical intensive care unit on day 7 with volume overload manifested by a 9.1-kg weight gain, bibasilar rales, elevated jugular venous pressure, a new S_3 gallop, and peripheral edema. A chest radiograph showed increasing pleural effusions and bilateral pulmonary edema. The patient required increasing amounts of dopamine—7 μg per kg per minute—to maintain a normal blood pressure.

Figure 1.—A photomicrograph of a typical area from the endomyocardial biopsy shows pronounced interstitial edema and myocardial eosinophilia, a nonspecific feature. No interstitial inflammation is detected. Small capillaries show endothelial cell prominence (hematoxylin and eosin stain, original magnification × 250).

Because a solitary serum creatine kinase level was elevated (382 IU per liter; normal range, 21 to 215) and the dependence on pressors persisted (>48 hours) after the cessation of IL-2 administration, the possibility of either IL-2–induced myocarditis or myocardial infarction was considered. Serial electrocardiograms showed nonspecific ST segment and T wave changes with decreased QRS voltage. Subsequent cardiac enzyme values were repeatedly normal. Creatine kinase fractionation consisted of 100% MM isoenzyme. An echocardiogram on day 8 showed mild four-chamber enlargement with a global decrease in left ventricular function. Segmental wall abnormalities were noted with hypokinesis of the septum and anterior and anterolateral walls, with a fractional shortening reduced at 22%. A right- and left-sided heart catheterization was done, including six right ventricular endomyocardial biopsies. Pulmonary artery catheter measurements showed a mean right atrial pressure of 9 mm of mercury and a moderately elevated right ventricular pressure (48/14 mm of mercury). Mean pulmonary artery pressures (34 mm of mercury), mean pulmonary capillary wedge pressure (26 mm of mercury), and left ventricular end-diastolic pressure (28 mm of mercury) were significantly elevated. Cardiac output as calculated by the Fick equation was 6 liters per minute (on dopamine therapy). The coronary arteries were angiographically normal.

A light-microscopic evaluation of the endomyocardial biopsy specimen showed marked interstitial edema with many extravasated erythrocytes. Capillary endothelial cells were diffusely enlarged and prominent. There was no evidence of myocardial infiltration by lymphocytes, neutrophils, or eosinophils (Figure 1). On immunofluorescent staining, no $CD4^+$ or $CD8^+$ T cells could be observed in the biopsy specimens, but there was accumulation of albumin and fibrin in the interstitium. Vascular endothelial cells were strongly stained by anti–HLA-DR antibodies. Electron microscopy showed pronounced interstitial edema with myocyte degeneration (Figure 2). This was characterized by myofilament

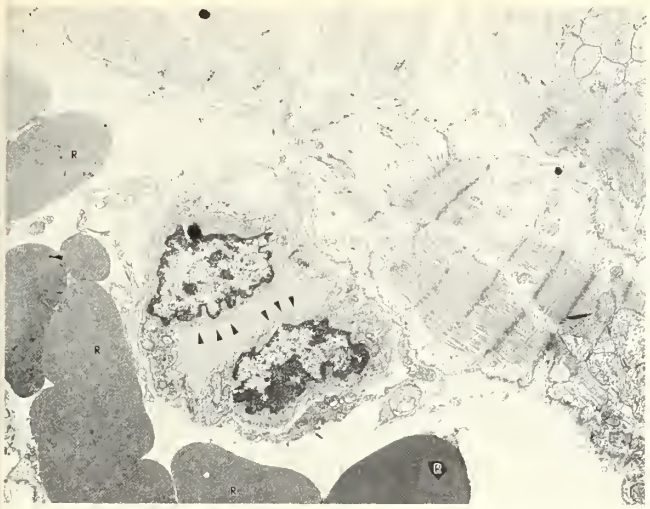

Figure 2.—An electron micrograph from a representative area shows prominent myofilament loss and endothelial cell alterations (**arrows**). Red cells (**R**) have extravasated into the interstitium. Myofilament loss is disproportionately of actin, leading to a coarse appearance of myofilaments remaining in the myocytes. Such a loss is most commonly associated with myocardial ischemic damage. Tissue was fixed in glutaraldehyde and then in epon, embedded in epon, and stained with uranyl acetate and lead citrate (original magnification × 10,000).

dissolution and clumping, dissolution of the sarcolemma, and homogenization of mitochondria. Surviving myocytes showed separation and coarsening of myofilaments. Capillaries demonstrated endothelial cell swelling. Inflammatory infiltrates were not found.

Leukapheresis was begun on day 8. Because of persistent congestive heart failure requiring dopamine and dobutamine infusions (each at 7 μg per kg per minute), the patient was considered to have a life-threatening toxic reaction from the IL-2 therapy and taken off protocol on day 8. Throughout her course, she remained afebrile without obvious infection. Surveillance blood cultures during the hypotensive episode showed no growth. No significant ventricular arrhythmias were recorded during the time she was monitored in the intensive care unit (days 8 through 11).

The rest of her hospital course was characterized by slow improvement. She was successfully weaned off pressor support by day 11. With pulmonary artery wedge pressures as a guide, volume overload was corrected using diuretics. Steroids were not used in the management of her congestive heart failure. On transfer to the ward (day 12), her weight was 2.72 kg above that at admission. Serial cardiac echocardiograms on days 10 and 13 continued to show diffuse hypokinesis and left ventricular dysfunction with no notable improvement in fractional shortening, consistent with minimally dilated cardiomyopathy. She was discharged from the hospital on day 14 on no diuretic therapy. A chest radiograph showed resolving bilateral pulmonary edema and a normal cardiac silhouette.

An echocardiogram done on day 36 continued to show global left ventricular dysfunction of the same magnitude as noted on previous studies, and she continued to have dyspnea with minimal exertion. All four echocardiograms showed globally abnormal wall motion, with fractional shortenings (a measure of left ventricular systolic function) of 22% to 23%. On day 59, the patient had a sudden cardiopulmonary arrest at home and could not be resuscitated by paramedics. No autopsy was done.

Discussion

The development of signs of congestive heart failure and persistent hypotension requiring pressor therapy for more than 48 hours following high-dose interleukin-2 therapy suggests the possibility of myocardial injury. The clinical differential diagnosis includes transient myocardial dysfunction due to IL-2 use, myocardial infarction, myocarditis, and now cardiomyopathy. Initial studies from the National Cancer Institute found a 4% rate of myocardial infarction in patients receiving high-dose IL-2 therapy.[1] The incidence of this complication has subsequently been reduced to less than 1% by a careful prescreening of patients for silent coronary artery disease.[10]

We have reported the occurrence of pathologically confirmed myocarditis in a patient in whom refractory heart failure developed following five days of high-dose IL-2 therapy.[11] More recently three additional cases of myocarditis following high-dose IL-2 therapy have been reported.[12,13] The overall incidence of confirmed myocarditis in IL-2–treated patients appears to be low—4 in more than 800 patients. Other cases of myocardial dysfunction have been reported, however, that were not evaluated by cardiac biopsy.[4]

This is a unique case of persistent cardiomyopathy associated with high-dose IL-2 therapy. An evaluation failed to detect risk factors for coronary artery disease, and evaluation after the onset of heart failure failed to provide evidence of myocardial ischemia or infarction. No identifiable cause for a dilated cardiomyopathy could be discerned in our patient other than recent IL-2 administration, although a recent viral infection with one of the cardiotropic viruses was not specifically excluded.[14] In contrast to previous reported cases of myocardial dysfunction occurring with IL-2 therapy, our patient did not have an obvious inflammatory or ischemic process. The pathologic findings of idiopathic dilated cardiomyopathy are nonspecific, however, and myocarditis may be missed by even several endomyocardial biopsies.[15] The pathologic findings of endothelial cell prominence, HLA-DR positivity, and the vascular leakage of fibrin and albumin seen in this patient's biopsy specimens are nonspecific and can be seen in cases of myocarditis or autoimmune disease affecting the heart. Ultrastructural features compatible with myocardial ischemic damage may have resulted from the vascular injury.

Finally, rather than returning to her pretreatment level of cardiac function with the discontinuation of interleukin-2, our patient continued to have both subjective and objective evidence of cardiac dysfunction as long as 36 days after the initiation of IL-2 therapy. Although the exact cause of death remains unknown, its sudden nature and the futility of resuscitative measures suggest a primary cardiac disorder.

A number of mechanisms may underlie myocardial dysfunction associated with IL-2 therapy. These include myocardial dysfunction due to increased interstitial edema. Myocardial depressant factors, similar to those observed in septic shock, may be released.[16] Secondarily released cytokines, including interferons and tumor necrosis factor, may contribute to myocardial dysfunction.[17] While these agents can contribute to reversible dysfunction during or immediately after IL-2 exposure, their role in causing permanent cardiac injuries is yet to be conclusively established. Cardiac toxicity due to myocardial ischemia has been ob-

served in clinical trials of interferon alfa (but not interferon gamma).[18,19] Although acute hypotension is the most common cardiovascular side effect of tumor necrosis factor-α,[20] a case of possible cardiomyopathy associated with prolonged treatment with tumor necrosis factor has been reported.[21] The effect of other cytokines that may be secondarily released following IL-2 administration—such as IL-1, IL-6 granulocyte-macrophage colony-stimulating factor, and IL-3—on the heart has not yet been adequately evaluated.[22,23]

We suggest that patients in whom congestive heart failure or a prolonged dependence on vasopressors develops after IL-2 therapy should be evaluated for myocardial damage due to ischemia, myocarditis, or cardiomyopathy. Assessing the levels of creatine kinase and its isoenzymes is helpful in detecting myocardial injury, as serum levels of this enzyme are usually decreased during IL-2 administration (W.E.S., J.H.W., E.R. Ashwood, MD, unpublished data, January 1989). Rises in the MB fraction may be observed following cardiac injury in IL-2-treated patients.[4,11] Electrocardiograms should be done to exclude ischemic changes. Echocardiograms may be useful in distinguishing between segmental wall motion abnormalities more typical of ischemia and global defects that represent diffuse myocardial processes (myocarditis and cardiomyopathy). Finally, because sepsis can present with hypotension, a search for infection should always be undertaken. We recommend the consideration of right-sided heart catheterization with myocardial biopsy in any patient receiving interleukin-2 in whom unexplained, persistent myocardial dysfunction develops. With this approach, the correct diagnosis can frequently be established and the possibility of infarction or ischemia can be reasonably excluded.

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Idiopathic Mediastinitis With Superior Vena Cava Obstruction, Cardiac Tamponade, and Cutaneous Vasculitis

JOHN M. LOEB, MD
Castro Valley, California

CHARLES M. LOMBARD, MD
Mountain View, California

We describe the case of a young woman who presented with cardiac tamponade and in whom a superior vena cava syndrome later developed, associated with a nodular, ulcerative cutaneous vasculitis. This case emphasizes the spectrum of fibrosing mediastinitis. Three similar cases of idiopathic fibrosing mediastinitis with vasculitis have been previously reported.[1-3] Systemic and localized vasculitis have been recognized more commonly in cases of retroperitoneal fibrosis and should be similarly recognized as part of the spectrum of fibrosing mediastinitis.[2,4]

Report of a Case

A 33-year-old woman was seen in October 1987 because of malaise and abdominal pain for a month, followed by cough, exertional dyspnea, and fever. The patient smoked cigarettes but otherwise was previously in good health and had taken no medications. On initial examination she was febrile and appeared ill with distended neck and superficial chest veins, supraclavicular adenopathy, a pericardial rub, hepatomegaly with a positive Kussmaul's sign, and a 20-mm pulsus paradoxus.

Leukocytosis, anemia, thrombocytosis, and a greatly increased sedimentation rate were noted. A chest x-ray film and echocardiogram revealed a large pericardial effusion. Signs of cardiac compression progressed; pericardiocentesis relieved the tamponade and yielded 300 ml of a sterile exudate with a low leukocyte count.

A computed tomographic (CT) scan of the chest (Figure 1) showed a diffuse nodular mediastinal and left hilar infiltrate suggestive of lymphadenopathy. An abdominal CT scan

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From the Eden Medical Center, Castro Valley (Dr Loeb), and the Pathology Department, El Camino Hospital, Mountain View (Dr Lombard), California.

Reprint requests to John M. Loeb, MD, 20097 Lake Chabot Rd, Castro Valley, CA 94546.

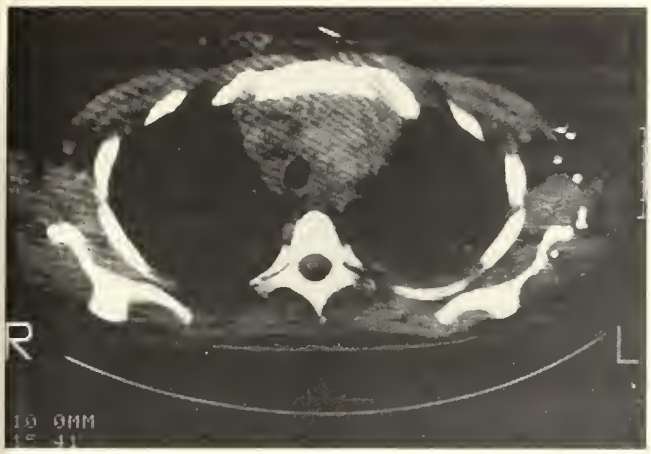

Figure 1.—A chest computed tomographic scan in October 1987 shows prominent enlargement of the upper anterior mediastinum with diffuse replacement of fat by soft tissue density infiltrate. Also seen are dilated left chest wall collaterals.

revealed hepatomegaly and pronounced periaortic and mesenteric adenopathy. A bone marrow aspirate revealed granulocytic hyperplasia. On mediastinoscopy the anterior mediastinal space was obliterated by dense adhesive inflammatory tissue. There was nonspecific reactive change of the supraclavicular and paratracheal nodes. Through a limited thoracotomy, a pericardial window was created, revealing an organizing fibrinous pericarditis. A biopsy specimen of the left lower lung showed a nonspecific chronic interstitial pneumonia and marked organizing pleural fibrosis.

The patient was anergic to a battery of antigens. Cultures of blood, marrow, lung, and lymph nodes were negative for bacteria, fungi, and acid-fast bacilli. Autoantibodies were not found; complement components were normal. Serologic tests for histoplasmosis, human immunodeficiency virus, *Coccidioides immitis* and *Legionella* and *Mycoplasma* species were negative. Epstein-Barr and cytomegalovirus serologic tests indicated past infection.

A regimen of methylprednisolone sodium succinate, 80 mg per day, was instituted parenterally, and systemic signs rapidly resolved. Prednisone therapy, 1 mg per kg per day, was continued as an outpatient. As the prednisone dosage was tapered to 20 mg per day, however, edema of the extremities, fatigue, and distension of the upper thoracic superficial veins increased; livedo reticularis and tender, erythematous nodules of the right hand, right buttocks, left thigh, and left ankle developed; and the lower extremity nodules ulcerated.

In June 1988, a magnetic resonance image of the chest showed superior vena caval obstruction with reconstitution caudally through the azygos vein and a large amount of adenopathy of superior mediastinal, precarinal aortopulmonary nodes. The pericardial effusion and hilar and left lower lobe infiltrate had resolved. An abdominal CT scan was now normal. Skin biopsies of the left foot and thigh revealed acute and chronic vasculitis involving arterioles (Figure 2).

Despite the development of ulcerative cutaneous nodules and symptoms of superior vena caval obstruction, the patient had no recurrence of serositis or fever. Hemogram and chemistry panel values and renal function were normal. The sedimentation rate was again increased. The prednisone dosage was increased to 60 mg per day, and azathioprine, 100 mg per day, was added. The lower extremity edema rapidly cleared. Cutaneous nodules regressed slowly and healed. The prednisone dosage was tapered slowly. Signs of the superior vena cava syndrome persisted despite several months of therapy with prednisone and azathioprine.

A CT of the chest in August 1988 revealed clearing of the originally noted mediastinal infiltrate compared with the appearance in October 1987, but numerous collateral veins of the chest, mild to moderate infiltration of the mediastinal fat with stranded and patchy densities consistent with fibrotic change, and obstruction of the superior vena cava were observed. It was elected to institute penicillamine therapy and to discontinue azathioprine. The penicillamine dosage was gradually increased to 750 mg per day while the prednisone dosage was maintained at an average of 20 mg per day. A chest CT scan in May 1989 revealed similar mediastinal changes compared with the August 1988 chest CT scan (Figure 3).

Penicillamine therapy was continued from October 1988 to September 1989. As the prednisone dosage was reduced to 10 mg per day, the cutaneous nodules progressed. Symptoms of the superior vena cava syndrome continued. In September 1989, penicillamine was discontinued and a regimen of hydroxychloroquine sulfate, 400 mg per day, was insti-

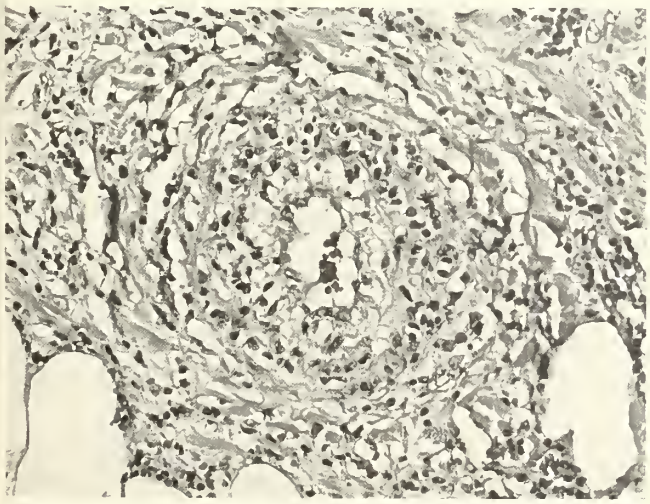

Figure 2.—An arteriole in the subcutaneous portion of a skin biopsy shows vasculitis with transmural infiltrate of inflammatory cells, predominantly lymphocytes and histiocytes (hematoxylin and eosin, original magnification × 250).

Figure 3.—A chest computed tomographic (CT) scan April 1989 shows compression of the superior vena cava and streaky fibrofatty mediastinal densities suggestive of fibrosis. Clearing of the mediastinum compared with the previous chest CT scan and chest wall collaterals are also evident.

tuted. Hydroxychloroquine therapy was discontinued after ten months because of a lack of effect on the cutaneous vasculitis.

In September 1990, the patient presented with recent gastrointestinal bleeding and severe anemia. An upper gastrointestinal endoscopy revealed varices of the proximal esophagus ("downhill varices"). Venography of the upper extremities showed total occlusion of both subclavian arteries as they drained into the superior vena cava, with abundant collaterals around the sites of obstruction. In addition, lower extremity venography and abdominal ultrasonography showed that the inferior vena cava was obstructed from the level of the confluence of the iliac arteries to just below the lower margin of the liver. The ureters were not obstructed.

As of August 1991, the patient is being treated with a regimen of hydrochlorothiazide and prednisone (10 to 20 mg a day) with methotrexate (7.5 mg a week) to control cutaneous vasculitis. There have been no other signs of systemic progression of her disease.

Discussion

We describe a case of a young woman with an acute, systemic inflammatory process who presented with an effusive, constrictive pericarditis that responded to pericardial stripping and corticosteriod therapy. Within the first six months of this disease process, she had the development of a superior vena cava syndrome due to extrinsic compression from mediastinitis, livedo reticularis, and an ulcerative, nodular cutaneous vasculitis. The patient has been observed for nearly four years and remains stable with a mild, compensated superior vena cava syndrome and limited cutaneous disease.

This patient clearly had an obliterative inflammatory process involving the mediastinum that caused obstruction of the superior vena cava. No drug, infectious, or neoplastic cause was found. As such, this process seems to fit best the spectrum of diseases known as "fibrosing mediastinitis," "sclerosing mediastinitis," or "idiopathic mediastinal fibrosis" in which any structure in the mediastinum, including trachea, esophagus, pulmonary artery, pulmonary vein, and superior vena cava, may become obstructed.[5] The frequency of the superior vena cava syndrome in fibrosing mediastinitis has in fact been found to be from 2%[6] to 12%[7] to 23%[8-10] of reported series.

The occurrence of a vasculitis, as seen in this case, in association with fibrosing mediastinitis has not been commonly recognized or emphasized. In a recent review of pulmonary vascular obstruction with fibrosing mediastinitis, the authors did not include systemic vasculitis.[11] In our review of the English language literature, we have found three previously reported cases of vasculitis in association with fibrosing mediastinitis.[1-3] As in our case, in each of these cases, ulcerative cutaneous nodules were described as features of the vasculitis.

Carton and Wong in 1969 first noted the association of vasculitis with fibrosing mediastinitis.[1] In this case, mediastinal and retroperitoneal fibrosis occurred in a 29-year-old man with superior vena caval obstruction. Arteritis was found in the retroperitoneum, sympathetic vessels, and peripheral small arteries and arterioles of the skin.

In 1981 Littlejohn and Keystone described the case of a young man with mediastinal and retroperitoneal fibrosis and a systemic vasculitis histologically found to involve the skin and mediastinum.[2] Pleuritis, pericarditis, and arthritis were also noted in this patient. In 1986 Fischer and DeLauney similarly described the case of a 29-year-old man with superior vena cava syndrome, livedo reticularis, and ulcerative cutaneous vasculitis. This patient also had retroperitoneal fibrosis.[3]

In our patient, the presenting problem was pericardial tamponade. This is the first report of cardiac tamponade as the initial manifestation of idiopathic fibrosing mediastinitis. In fact, Barrett has reported that mediastinal fibrosis does not invade the pericardium.[12] Others, however, have noted the presence of pleural and pericardial effusions in patients with fibrosing mediastinitis, including the case described by Littlejohn and Keystone and three other cases of mediastinitis without vasculitis in which pericardial thickening or pericardial effusions were noted.[2,13-15] Pericardial disease clearly should be recognized in the spectrum of fibrosing mediastinitis.

The concomitant occurrence of mediastinitis, serositis, and vasculitis can probably be better appreciated by considering the relationship of idiopathic fibrosing mediastinitis to idiopathic retroperitoneal fibrosis. Koep and Zuidema reviewed nearly 500 cases of retroperitoneal fibrosis and found a 3.3% incidence of mediastinal fibrosis.[4] In fact, all three of the cases of mediastinitis with vasculitis noted earlier were also associated with retroperitoneal fibrosis. The recognition that inflammatory fibrosis may occur in more than one organ system or region has led some authors to consider these to be a family of disorders known as "multifocal fibrosclerosis" or "systemic fibrosclerosing syndromes."[1,3,15] Ureteral obstruction from the retroperitoneal process has not developed in our patient, but she was later found to have an inferior vena caval obstruction. She did initially present with periaortic and mesenteric adenopathy and clearly also has had a retroperitoneal inflammatory process.

As to the relationship of vasculitis to retroperitoneal fibrosis, Littlejohn and Keystone noted a 7% prevalence (37 cases) of histologically defined vasculitis in a literature survey of about 500 cases of retroperitoneal fibrosis.[2,4] Of these 37 patients, 30 (81%) had vasculitis in both retroperitoneal and distal sites. The authors suggested that the combination of retroperitoneal and mediastinal fibrosis with cutaneous vasculitis may represent a distinct subset of idiopathic fibrosis seen in young men. The case reported herein of a young woman with mediastinitis and cutaneous vasculitis seems to fall within the spectrum of this subset.

Autoimmune diseases and several other idiopathic, immune-mediated inflammatory disorders have also been associated with retroperitoneal fibrosis. The list of associated disorders includes systemic lupus erythematosus, scleroderma, eosinophilic fasciitis, amyloidosis, and crescentic glomerulonephritis.[16-23] These interrelationships point to a common immune-mediated pathogenesis. Fibrosing syndromes have been linked to other causes including underlying malignancy, infection (particularly granulomatous), a history of drug ingestion (methysergide or other vasoactive pharmacologic agents), trauma, and atherosclerosis.[15,17]

Clearly many causes may trigger similar pathogenetic mechanisms resulting in an inflammatory cellular response and fibrosis. In situations, however, such as our case in which no antigen or defined triggering event can be identified, the precise mechanism of fibrosis and inflammation can only be speculative. Nevertheless, this case serves to empha-

size the breadth of associations of mediastinitis, in particular to add to the recognition of the link between vasculitis, cardiac tamponade, and superior vena caval obstruction.

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Home Treatment of Calf Deep Venous Thrombosis

CYRIL BRUCE CALLISTER, PA-C
STEPHEN DANIEL WOOD, MD, MSPH
Salt Lake City, Utah

GEORGE L. WHITE, Jr, PA-C, PhD, MSPH
Hattiesburg, Mississippi

ELIZABETH D. TUCKER, RN
Salt Lake City, Utah

TRADITIONAL THERAPY in the United States for deep venous thrombosis confined to the calf involves seven to ten days of stay in hospital, but British practice advocates only three days.[1] Recent Canadian experience advocates five days of hospital stay to begin anticoagulant treatment.[2] An otherwise healthy 37-year-old man was successfully treated at home for seven days with a continuous intravenous infusion of heparin. There were no complications during or following treatment, and the patient recovered uneventfully. Cost savings of approximately $4,000 were realized by avoiding admission to hospital.

(Callister CB, Wood SD, White GL Jr, Tucker ED: Home treatment of calf deep venous thrombosis. West J Med 1991 Sep; 155:299-300)

From the Foothill Family Clinic (Mr Callister and Dr Wood); the Physician's Assistant Program (Mr Callister), Departments of Family and Preventive Medicine (Mr Callister and Dr Wood) and Ophthalmology (Dr White), University of Utah School of Medicine; and the New England Critical Care (Ms Tucker), Salt Lake City. Dr White is currently with the Center for Community Health, Department of Health Education, College of Health and Human Sciences, University of Southern Mississippi, Hattiesburg.

Reprint requests to Bruce Callister, PA-C, Foothill Family Clinic, 2295 S Foothill Dr, Salt Lake City, UT 84109.

Report of a Case

The patient, a 37-year-old healthy, nonsmoking, male graduate student, was referred to our family practice clinic for the evaluation of left lower leg pain of a week's duration. His history did not reveal trauma, overexertion, periods of prolonged immobility, or a surgical procedure. He had, however, been admitted to hospital 15 years ago for bilateral thrombophlebitis of the upper legs. He suffered no sequelae from this episode and had had no medical problems until now.

On physical examination, his left calf was exquisitely tender with a positive Homan's sign. Superficial varicose veins were noted on the posterior aspects of both legs. The left calf was without erythema or swelling and did not appear excessively warm to touch. Calf diameter measurements were equal. Femoral, dorsalis pedis, and posterior tibialis pulses were strong and equal bilaterally. The lungs were clear to auscultation, and the heart was normal.

A Doppler ultrasonogram of the left leg revealed the paired peroneal veins in the left calf to be thrombosed. The thrombosis was confined to the peroneal veins. A diagnosis of deep venous thrombosis of the left calf was made. The patient was determined to be a good candidate for outpatient therapy and was willing to try it (Table 1). A home infusion therapy company (New England Critical Care, Westboro, Massachusetts) was contacted to arrange treatment. The initial home nursing visit consisted of a physical assessment; baseline prothrombin time, partial thromboplastin time, and complete blood count; and patient education. Potential problems and side effects related to deep venous thrombosis and anticoagulation therapy were discussed with the patient. After obtaining signed, informed consent, we established venous access in a peripheral vein, and a portable controlled infusion device (Pharmacia Deltec CADD-1) was attached for anticoagulation therapy. Heparin therapy was initiated with a 5,000-unit bolus, followed by 1,000 units per hour by continuous intravenous infusion. Oral anticoagulant medication—warfarin sodium, 10 mg once a day—was also started simultaneously. The nurse made twice-a-day visits to the patient's home to monitor progress and obtain blood specimens.

The laboratory results were reported to the physician, and appropriate changes in heparin dosage were made to keep the partial thromboplastin time between 1.5 and 2.0 times the control value. Similarly, the warfarin dosage was adjusted to keep the prothrombin time in the accepted therapeutic range of 1.2 to 1.5 times the control value.

The patient completed seven days of therapy in this manner. Clear lines of communication between the home infusion therapy team and the attending physician were maintained. The patient's venous access remained patent and without inflammation throughout treatment. He had no adverse effects from heparin and fully recovered from his calf vein thrombosis. Maintenance warfarin therapy was continued for three months with periodic monitoring at the clinic to

TABLE 1.—*Selection Criterio for Home Infusion Therapy Using Heporin for Colf Deep Venous Thrombosis (DVT)*

Acceptance Criteria	*Contraindications*
Patient reliability	Intracranial neoplasm
Suitable home environment	Other malignant neoplasms
Electricity, running water, and a clean living space	Stroke within 2 months
Access to emergency medical services	Active bleeding (any source)
Appropriate space for infusion supplies	Preexisting hemorrhagic disease
Lives within a reasonable distance of home health nurses and emergency medical services	Recent operation
Able to care for self, and another competent care person is in the home	History of alcoholism or liver disease
Normal cardiopulmonary function	
Documentation of isolated calf DVT	
Patient preference for outpatient regimen	
Consistent intravenous access	

TABLE 2.—*Cost of Home Treotment Versus Hospitol Treotment of Colf Deep Venous Thrombosis*

Treatment Option	*Length of Treatment, d*	*Daily Rate, $*	*Completed, $*
Home therapy	7	263	1,841
Inpatient*	7	832	5,824
DRG code 131	6	455	2,732

DRG = diagnosis-related group

*University hospital.

assure that his prothrombin time was in the therapeutic range. A follow-up Doppler ultrasonogram was not done.

Discussion

This report illustrates the use of home infusion therapy for the treatment of deep venous thrombosis confined to the calf as an option to hospital admission in carefully selected, otherwise healthy patients. Patients with underlying disease or risk factors contraindicating anticoagulant therapy are not candidates for this treatment option.[2,3] Because some below-the-knee thrombi might embolize before therapy, a lung scan should be considered. Patients with positive lung scans should not be treated at home.

The treatment of deep venous thrombosis below the knee varies from full anticoagulation for seven to ten days to simply observing a patient with noninvasive tests, treating only those patients whose thrombi propagate proximally.[3,4] Serial impedance plethysmography (IPG) monitoring without therapy is one such approach.[4] In the United States, anticoagulation therapy in a hospital setting has been the traditional and accepted norm.[1,4] In Europe, however, home treatment using subcutaneous heparin has been successfully implemented.[5] Regardless of the route of heparin administration, it is important to define objectively the location of the thrombus. Venography and IPG are superior to Doppler ultrasonography in diagnosing calf deep venous thrombosis.

The frequency of pulmonary emboli originating from isolated calf deep venous thrombi is controversial.[4,6] One small, retrospective study without controls showed that 13% of cases of fatal pulmonary emboli originated in the calf.[6] Other studies have shown that the incidence of fatal pulmonary emboli from a distal deep venous thrombus is low.[3,4] Philbrick and Becker thoroughly reviewed the literature regarding this disorder, which can be extrapolated to provide the basic rationale for home treatment.[3] Calf deep venous thrombi extend proximally to the thigh in about 10% of symptomatic patients. This propagation occurs before embolization. No fatal emboli were reported in patients with deep venous thrombosis confined to the calf.[3] Traditional anticoagulation treatment with heparin and warfarin for symptomatic patients with calf thrombi prevents extension, embolization, and early recurrence.

Pulmonary emboli and the risks of bleeding from heparin therapy are valid concerns when treating calf deep venous thrombosis, especially in the home. The greatest risk of not treating this disorder is the development of pulmonary embolism.[7] There are about 500,000 cases of pulmonary embolism a year in the United States, resulting in more than 50,000 deaths.[8] The risk of major bleeding from anticoagulation in patients with deep venous thrombosis has been said to be less than 10% and is usually associated with an underlying risk factor such as a recent operation or cancer.[3,4] If bleeding or embolism occurs in a patient treated at home, physicians must be prepared to face possible medicolegal questions because the current standard of care is in-hospital care.

If home treatment is considered, an experienced home health care agency should be chosen so this approach can be implemented safely. A suitable home environment is also necessary (Table 1).

The case presented here illustrates an alternative treatment regimen for deep venous thrombosis confined to the calf and supporting rationale. A cost comparison of seven days of home treatment and seven days of hospital care (Table 2) reveals substantial savings. Because the safety of home treatment of calf thrombi has not been fully validated, a larger series of cases will be needed to further assess the appropriateness of this therapeutic option.

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Radiologic Case

A 3-Year-Old Boy With Neck Pain After Motor-Vehicle Accident

WAZHMA ASLAMY; KELVIN DANIELSON, MD; SAMUEL J. HESSEL, MD; *and* JONATHAN M. LEVY, MD, *Scottsdale, Arizona*

A "Radiologic Case" is published in this format on a regular basis. Physicians interested in contributing to the series are encouraged to send their radiologic cases to the series' editor.

JONATHAN M. LEVY, MD
Assistant Editor

A 3-year-old boy complained of neck pain after a motor-vehicle accident. He was awake and alert, with no obvious injuries. On physical examination, he had mild tenderness to palpation over the back of his neck. Because of the findings, x-ray films of the cervical spine were obtained. The odontoid view (Figure 1) appeared abnormal.

What is the abnormality?

How would you verify the findings?

How would you treat this patient?

SEE FOLLOWING PAGE FOR DIAGNOSIS AND DISCUSSION

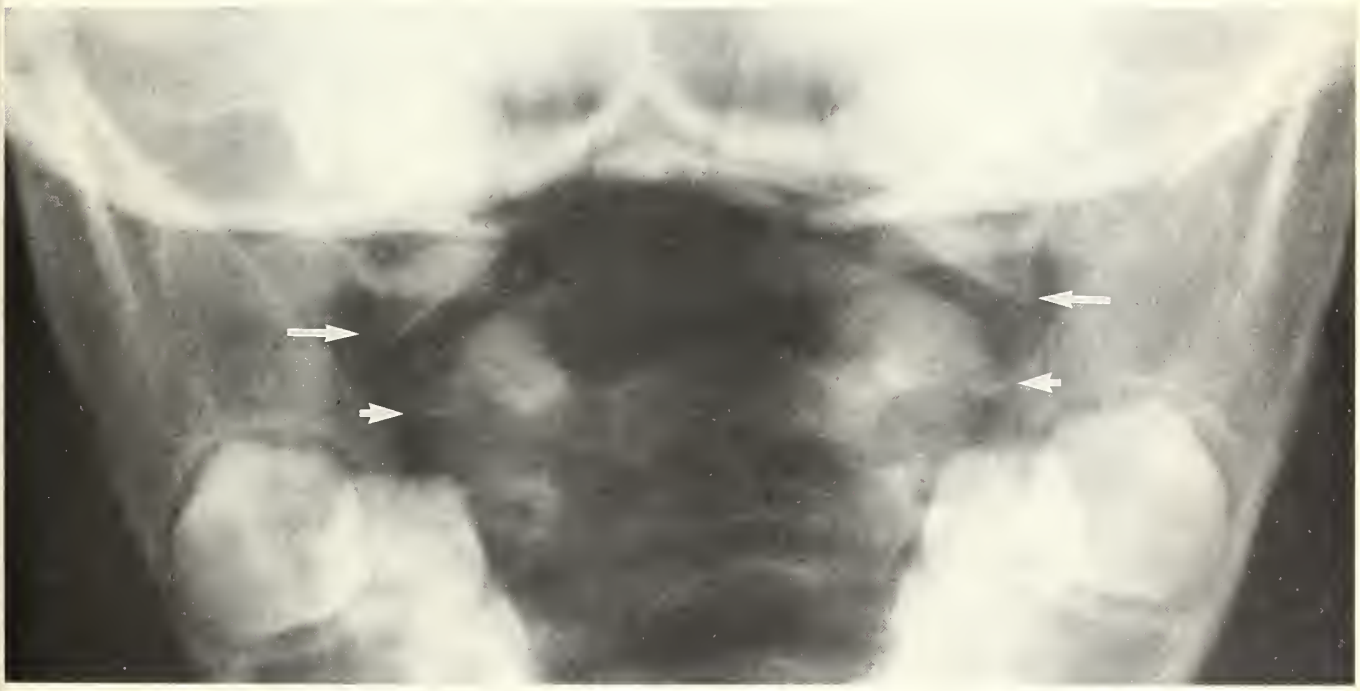

Figure 1.—An odontoid view of the cervical spine shows the relationship of lateral masses of C-1 **(long arrows)** and C-2 **(short arrows).**

(Aslamy W, Danielson K, Hessel SJ, Levy JM: A 3-year-old boy with neck pain after motor-vehicle accident. West J Med 1991 Sep; 155:301-302)

Ms Aslamy is a fourth-year medical student at the University of Arizona School of Medicine, Tucson. From the Department of Diagnostic Radiology, Scottsdale Memorial Hospital, Scottsdale, Arizona (Drs Danielson, Hessel, and Levy).

Reprint requests to Jonathan M. Levy, MD, Department of Diagnostic Radiology, Scottsdale Memorial Hospital, 7400 E Osborn Rd, Scottsdale, AZ 85251.

ANSWER: Pseudospread of the atlas

THE FRONTAL VIEW of the cervical spine (odontoid view) shows widening of the lateral masses of C-1 when compared with C-2 (Figure 1). In an adult, these findings would indicate the likelihood of a Jefferson fracture in which a compressive force on the cervical spine fractures the arch of C-1 and spreads the lateral masses. In children younger than 4 years, however, pseudospread of the atlas should be considered in the differential diagnosis. When the child's films were reviewed by a radiologist, a computed tomographic scan of the upper cervical spine was suggested. This showed a normal developmental C-1 arch, with no evidence of fracture (Figure 2).

Apparent spreading (pseudospread) of the atlas most likely results from a discrepancy in the growth rates of the atlas and axis. In the first year of life in affected persons, the transverse diameter of the atlas increases at a rate faster than that of the axis. A prominence of the inferolateral aspect of the atlas may develop. The asymmetric appearance gradually disappears by age 3 or 4, although significant asymmetry has been documented in a child as old as 5 years 8 months.

Jefferson fracture is rare in children. This is thought to be due to age-related factors such as flexibility of the vertebrae and intervertebral ligaments of children's spines and a lower exposure level to industrial trauma. In addition, the pathophysiology of Jefferson fracture depends on axial loading of the skull vertex with the head and neck held rigidly erect. Children are more tolerant of this type of force because of their lower weight and higher skull plasticity. The synchondroses of C-1 (see Figure 2) may also serve as an elastic buffer in children.

When clinical and plain film findings suggest the diagnosis of pseudospread of the atlas, computed tomography can exclude injury by demonstrating an intact bony ring. Our patient was shown to have a "normal" atlas and was sent home with his parents.

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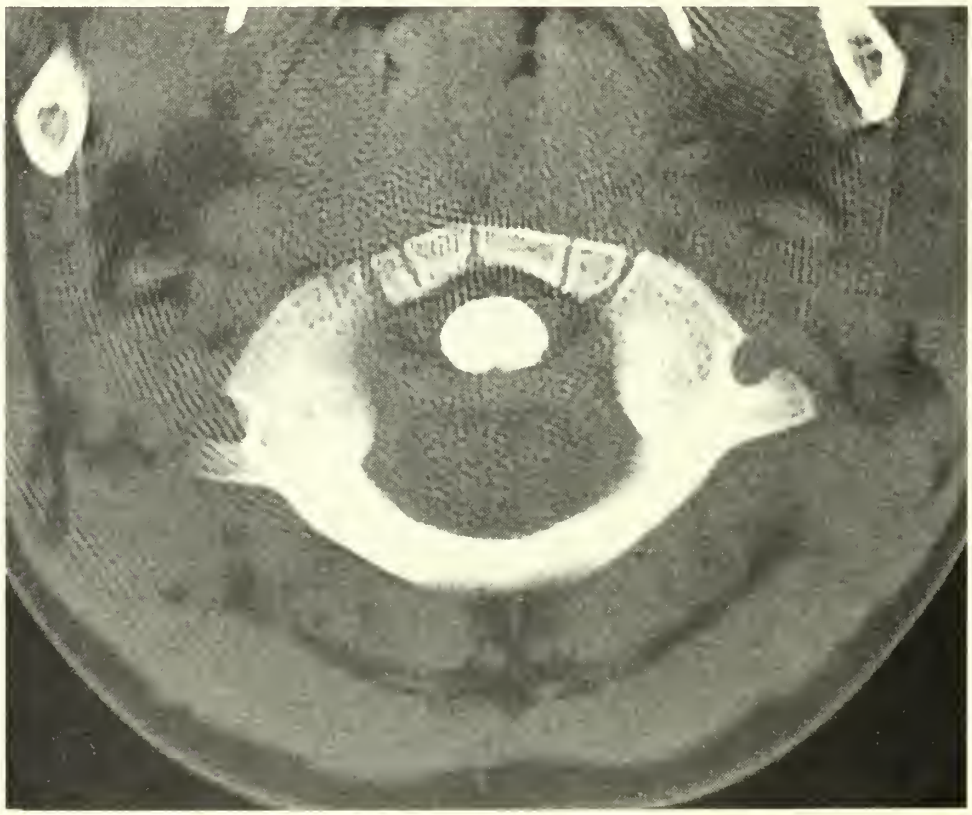

Figure 2.—A computed tomographic scan of the arch of C-1 shows normal growth centers. There is no spreading of the arch.

Commentary

Partnerships for Improving Border Health

ELENA O. NIGHTINGALE, MD, PhD, *Washington, DC, and* MAGDA G. PECK, ScD, PA, *Omaha, Nebraska*

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The United States and Mexico share the longest border in the world between a developed and a developing nation. Nearly 65 million people populate the four US and six Mexican border states, and more than 9 million live in the communities along the border.[1] The health of this unique, binational population is of increasing concern to a broader range of persons and institutions on both sides of the border. As participation in the partnership required for successful border health solutions grows, two newer players—health professional organizations and private foundations—must examine their respective and synergistic roles.

What Health Professional Organizations Can Do

Health professional organizations in the United States, particularly the medical associations of the states at the border, have not ignored the health needs of the border populations. But health professional organizations and their members as individuals can also use their skills to promote health by working to protect the health and human rights of all persons in their localities.

Human rights are divided into civil and political rights, which in our society take priority, and social, economic, and cultural rights, which take second place. Our country subscribes to the belief that without civil and political rights, no other rights, such as the right to health care, can be upheld. This view is not completely shared by other countries or by our own population. For example, public opinion polls have shown that 90% of Americans support health services for all children.[2] The growth of homelessness in the United States is another example of a violation of a basic human right. All human rights need to be honored—not some at the expense of others.

The human rights of many people are being violated in different ways on both sides of the border, and these violations have repercussions for health. Undocumented aliens cross to the United States in large numbers and at times with great risk. Many come not only for social and economic reasons but also for political reasons. Often they are refugees from repression and civil wars in Central and South America. Once in this country, for many the establishment of refugee status is the only way to survive, for repatriation means detention, torture, and even death. In addition, while held in camps, refugees' multitude of health problems may be poorly attended to and, all too often, children who are on their own are held in adult facilities without appropriate services.

The border has been plagued by increasing rates of violence, and the results of rape and brutality eventually come to emergency services. There are also accusations of violence committed by the border patrols; the American Friends Service Committee documented 380 cases of human rights abuses by border patrol agents against immigrants in 1989.[3] There is a growing climate of intolerance of Hispanics in the United States, and there is serious concern about the violation of human rights of Mexicans living here. This climate inevitably leads to rising levels of violence and therefore of serious injury and even death. Thus, attention to human rights needs to be increased in the border area, and health professionals have an important role.

Many health professional organizations have formed human rights committees. These committees usually have started in the international sections of their organizations. They have worked on civil and political abuses of patients or of health professionals themselves. So, for example, the American Academy of Pediatrics has worked to educate its members on violations of the human rights of children and the role that the American Academy of Pediatrics can play toward increasing support for the United Nations Convention on the Rights of the Child.

State medical associations can, through educational activities, meetings, publications, and site visits, increase the visibility of the plight of refugees. They can collaborate with lawyers' human rights organizations on documenting physical abuse that would help to establish refugee status. They also can establish networks of physicians who are willing to learn about and treat persons who have been victims of torture or extreme deprivation and who now reside within their communities. Recognizing a history of abuse in a patient seeking treatment for headache or insomnia, for example, requires an awareness of the political situation in the country of origin and of the possibility of a history of torture. The ability to elicit such a history without harming the patient needs to be developed.

It is not necessary to go to other countries or to go far afield to become more active in the support of human rights of people who have sought refuge from countries where basic human rights are not observed, including, for example, Guatemala and El Salvador. For instance, women who are detained for political reasons are commonly raped. Treating these women refugees is difficult, long term, and essential, and gynecologists and mental health professionals need to collaborate in this endeavor.

(Nightingale EO, Peck MG: Partnerships for improving border health. West J Med 1991 Sep; 155:303-305)

From the Carnegie Corporation of New York, New York (Drs Nightingale and Peck), and the Department of Pediatrics, University of Nebraska Medical Center, Omaha (Dr Peck).

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Reprint requests to Elena O. Nightingale, MD, PhD, Carnegie Corporation of New York, 2400 N St NW, 6th Floor, Washington, DC 20037-1153.

Passive bystanders—whether local or at a distance—allow atrocities to occur through their lack of protest, which is taken as evidence of agreement by the perpetrators. On the other hand, the power of a collective voice on behalf of human rights and the ethical practice of medicine is great. A network of colleagues provides not only people to do the work but also emotional support and confirmation of the value of human rights work.

Health professional organizations can work toward improving the health of the border populations by establishing the right to health care and enforcing that right through universal access to care. Lobbying for effective federal legislation to guarantee health care as a right is an important role for health professional organizations. Securing the right to health care is not enough, however. In Mexico, all citizens have a legislated right to health care, although appropriate care is not universally available. While the Mexican health care system has a comprehensive infrastructure dedicated to serving the uninsured, resources often are inadequate to meet the need for services. Health professional organizations can become powerful voices for action at all levels of government and for promoting binational collaboration to improve access to quality care on both sides of the border. We have much to learn from each other.

What Foundations Can Do

The current configuration of institutions and individuals located at the border or with interest in border health is complex and congested. Public—local, state, and national—and private health care professionals on both sides abound in some areas and are scarce in others. The face of industry and business continues to grow and change; the dramatic proliferation of *maquiladora* ("assembly") plants in northern Mexico exemplifies this transition. The impending free trade agreement will have a substantial effect on health-related concerns, such as environmental and occupational hazards. Academic centers, including colleges and universities, on both sides are an important force. International agencies, such as the Pan American Health Organization and the United States-Mexico Border Health Association, provide some umbrella mechanisms. Each has its own agenda and perspective, its own political and cultural vantage points, and its own perception of "border." All generally agree that there are many problems in health, and most agree that these problems are worsening.

Several questions emerge:

- Is there a unique role that foundations can play amidst this complex configuration?
- Where can and should large foundations fit in this landscape? Is the role any different at the United States-Mexico border from other areas of the country or the region? and,
- Should expectations of national, state, or local foundations or the boundaries within which they normally operate be relaxed or changed to accommodate special conditions at the border?

Health problems at the US-Mexico border have reached crisis proportions. In the United States money coming from state and federal sources is insufficient and unlikely to increase. The greatest share of the burden for the cost of providing health services must inevitably fall on the public sector. Secretary of Health and Human Services (HHS) Louis Sullivan's challenge of the 1990s is serving all Americans. A major goal of HHS for the year 2000 is to decrease the disparities in health between majority and minority populations. Unfortunately, the emphasis is on personal responsibility for health, without a commitment of federal resources sufficient to enable disadvantaged persons to assume such responsibility.

While HHS admits the need to change the environment of the neediest people to improve their health, the burden of change is placed on states and communities. No foundation or even a consortium of foundations has sufficient funds to deliver health services for the long term. Through public and private partnerships, formal and informal, it is possible to enhance greatly what the public sector is able to do, however. Collaboration and cooperation among public and private groups is key to effecting change in the US-Mexico border region.

National foundations do have important roles to play at the border. Foundations are free of the constraints of government and represent only themselves. In the international scope of US-Mexico border activities, foundations are more independent than other umbrella groups such as the Pan American Health Organization or the US-Mexico Border Health Association. This injects an evenness in the complex configuration that keeps the interest of improving health above the fray. Moreover, there are few health umbrella groups, so foundation involvement can facilitate "big picture" approaches and the building of bridges between groups and sectors. Further, in the international arena, some foundations are well known and give credibility to the activities and institutions supported.

Larger foundations or consortia of foundations usually can direct sizable amounts of money at a focused effort (such as research), something that is beyond the scope or capacity of most other regional players, which often provide only leverage money. Foundations can also provide some financial support for infrastructure development. For example, in the initial phase, the Mexican Foundation for Health used private foundation dollars from the United States to support the basic growth and development of the foundation itself, which in turn has led to many other sources of funding and more self-sufficiency. This could be a model for other foundations.

A foundation can promote a particular health agenda such as maternal and child health or the health of women working in *maquilas* and insure its priority amid changing conditions and circumstances. Foundations can have a convening function to link policy, research, and practitioner communities. These meetings can be important to bring other activities to fruition or to produce new ideas. They also help develop policy and identify research needs. Foundations can publicize and disseminate ideas and findings and can stimulate public and private sectors to increase efforts in a particular direction.

The work of national foundations concerned about health in the border region can be enhanced through cooperative relations with nongovernmental community organizations and medical societies. Traditional public health interventions supported by foundations often are channeled through public-sector institutions where support and participation are usually forthcoming. Many families who live on both sides of the border rely on private practitioners for health care, however. Medical societies can provide access to private physicians to solicit and engage their interest, ideas, and participation.

Medical societies also can provide the political will necessary to launch community-based interventions supported by foundation funds. In turn, foundations can augment the work of professional medical societies. Limited financial support for new initiatives to improve health is one option. But more important, foundations can contribute to the work of medical societies by acting as catalysts for change through the promotion of increased physician awareness about the special needs and circumstances of the US-Mexico border population.

Building Partnerships—Linking Foundations and Health Professionals

Foundations and health professional organizations can join forces to improve health. Although each foundation has its own rules and guidelines, events can influence the creation of new programs. Thus, a health crisis along the border may be used to mobilize foundation support at the local, state, and national levels and to create new funding partnerships. Fiscal marriages can ground a project nicely.

Some of the large national foundations have expressed an interest in global environmental issues. It might be possible to capture this interest for the particular environmental needs along the border. Some foundations operate only within states or communities. The Foundation Center, with offices in New York City and Washington, DC, has directories of foundations by geographic area and a listing of foundations that have given grants in health. The Foundation Center can assist those who would like to identify sources of support for research, communication, and other health-related agendas along the border.

Whether publicly or privately funded, health research should be undertaken only if the results are used to benefit and strengthen the study population and mechanisms are built in to implement those parts of the project that work well. Otherwise, demonstration and research projects to improve health will raise community expectations, only to dash them when the project is over. From past experience, it is clear that there should be the same expectations of process and product and of monitoring and evaluating at the border as elsewhere. More attention should be paid to providing technical assistance for development of proposals and projects. There is also a need for binational cultural and language sensitivity compatible with these goals and with the quality of the work.

Medical societies' access to private physicians can be used to raise the awareness of physicians of issues such as health and human rights at the border, or to reach policymakers on border health care issues. The societies can also gain the support of private physicians for particular demonstration or research projects to promote health. With respect to health at the border, medical societies' efforts can help physicians to pay particular attention to specific problems, to think more broadly, and to join with other sectors in efforts to improve health.

If the health and well-being of the millions of families and children living on the border of the United States and Mexico are to improve, basic human rights, including health, must be respected and protected. Key persons and institutions from the private sector must both acknowledge existing or increasing health problems and be a part of creative, multifaceted solutions. Health professional organizations and private foundations, separately and together, can play important roles in fostering change towards health as well as human rights in this unique and increasingly important geopolitical region.

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Editorials

Border Health Spans the Continent

In this issue Elena Nightingale, MD, reports findings and makes recommendations about "border" health problems.[1] These problems grow and spread as poverty, tensions, and violence grow and spread. The border is not simply a line but a region and perhaps a condition. Every day, political and economic refugees enter the United States from Mexico and Central America. They travel extensively. Physicians in all parts of the country need to appreciate and act on the issues Dr Nightingale presents.

A student and I recently saw a patient in a clinic at the University of California, San Francisco. The 65-year-old widow, visiting from El Salvador, had head, shoulder, and back pain. The usual history was not remarkable, and there were no positive physical findings. Through a translator, I asked about her experiences in the war. She said that several of her young relatives had disappeared and that she worried constantly about the others. She felt that army helicopter gunships were far more terrifying and unpredictable than guerrillas. She herself had associated flares in her symptoms with increased disruption caused by the war. She wondered if her pain could be related to fear. Later, when I asked about her sleep patterns, she said, "I have terrible nightmares when I am in this country." What about when she is in El Salvador? "There, I don't sleep at all."

Border health is part of physicians' practices wherever they may be. We need to be alert to subtle wounds caused by the effects of civil unrest on noncombatants. We need to work toward humane refugee and foreign aid policies that encourage good health.

LINDA HAWES CLEVER, MD

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How We Get Stoned

In the Hippocratic oath, physicians swear by various deities that "I will not cut persons laboring under the stone, but will leave this to be done by men who are practitioners of this work." Unfortunately, many still labor under the stone. The practitioners of this work, our urological colleagues, are increasingly armed with powerful new technologies for fragmenting and removing kidney stones, but these concretions remain as important sources of morbidity, if rarely of mortality.

The kidney is the master organ of homeostasis, guarding as it does the sanctity of the extracellular fluid, our "internal environment" (Claude Bernard). Renal microtitration of fluid, electrolytes, and metabolic constituents in the extracellular fluid comes at a cost. Urine composition must vary widely to accomplish this feat of homeostasis in the face of diverse dietary and metabolic challenges. The urine, né altered extracellular fluid, must then remain fluid and sterile in its long, slow passage between the ostia of the collecting tubules and the urethral meatus. Over the years, renal physiologists and internists have extensively studied the homeostatic role of the kidney, and urologists have become increasingly skilled in maintaining the patency of the outflow pathway. Less attention, however, has been directed to what might be called the conduit chemistry of the urine itself.

In the study of kidney stones, a large number of approaches have been used. The epidemiology of stone diathesis is fascinating, albeit not very revelatory. "Stone belts" have been described in the United States and elsewhere without clear-cut demonstrable causes in soil, climate, or population ethnicity. Stone epidemics have also occurred, with both waxing and waning. For example, in the Norfolk and Norwich Hospital in England, 1 in every 38 patients admitted between 1772 and 1816 had a bladder stone.[1] Samuel Pepys, the diarist, exhibited his tennis ball-sized bladder stone annually at a special party at which the various calculi of the guests were admired. This type of stone has virtually disappeared in the West but has remained a problem in Southeast Asia.

It has also long been evident that stone diathesis may be familial. A number of genetic diseases may be primarily or exclusively manifested by the occurrence of kidney stones. Among these are cystinuria, primary hyperoxaluria (types 1 and 2), genetic forms of gout, the Lesch-Nyhan syndrome, xanthinuria, familial renal tubular acidosis, adenine phosphoribosyl-transferase deficiency (2,8-dihydroxyadenine stones), and probably many cases of idiopathic hypercalciuria. In some of these disorders, the explanation of stone pathogenesis is immediately apparent from a specific enzymatic abnormality. In others the link is not yet elucidated. Beyond these specific disorders, there are families with a stone diathesis, usually calcium oxalate in composition, for which no specific metabolic disorder has been defined.

In the study of stone pathogenesis, it is useful to consider two categories of variables: factors that result in increased concentrations in the urine of the crystalloid components of stones, and physicochemical changes in the urine (or urinary tract) conducive to stone formation at normal concentrations of crystalloids.[2] In the past, major attention has been largely directed to the first category because crystalloid concentration is the obvious driving force for the precipitation of stone constituents. The concentration of crystalloids in turn depends on two variables: the absolute amount of the substance excreted per unit of time and the volume of water in which that excretion occurs. Volume manipulation is a simple but important and often-neglected therapeutic maneuver in stone prophylaxis. Among the earliest investigations of a patient with a stone are determinations of whether there are increases in the excretion rates of these crystalloids, especially calcium, oxalate, cystine, uric acid, or ammonia (from urea-splitting organisms in infected urine).

The second category of stone pathogenesis—the variables other than crystalloid concentration—is less well understood. Urine pH may alter the effective concentration of a crystalloid (especially uric acid and magnesium ammonium phosphate). Stasis may allow time for the slow accretion of stone growth. It seems likely that many embryonic stones are harmlessly aborted through the urinary stream, as witnessed by crystal aggregates in a concentrated morning specimen. The possible pathogenetic role of abnormal stone matrix is still being investigated. The presence of a foreign body, most frequently another stone or even a few crystals, may serve as

a nidus of crystallization through the phenomenon of epitaxy. Perhaps of greatest importance, however, is the presence of protective substances in normal urine.

Do protective substances exist as natural water softeners in normal urine? Clearly they do. We daily excrete amounts of calcium, oxalate, and phosphate that cannot be dissolved in 1 to 2 liters of distilled water. In its wisdom the body has evolved mechanisms to maintain the metastability of these and other components in solution in the urine. Some of the participants in this protective system have long been known—citrate, magnesium, pyrophosphate, for example. Other components have been more newly discovered, or their potential roles more newly appreciated, such as the Tamm-Horsfall protein and nephrocalcin. The latter glycoprotein is particularly interesting because it is specifically synthesized in the renal tubule and contains the remarkable calcium-binding amino acid, γ-carboxyglutamic acid, the synthesis of which requires vitamin K. Patients with stone diathesis who do not exhibit excessive urinary concentrations of the offending crystalloids may well have abnormalities of these protective substances. It is intriguing to think that in the future it may be possible to increase urinary protective mechanisms and to decrease urinary crystalloid concentrations in the prophylaxis of stone growth or recurrence.

In this issue of the journal, Roger Sutton, DM, presents an interesting overview of the many aspects of stone pathogenesis, an area in which he has long had interest and to the understanding of which he has made many personal contributions.[3] The number of topics surveyed in this brief presentation reflects the extraordinary heterogeneity of this discipline—oxalate metabolism, calcium metabolism, urinary protective substances, primary hyperparathyroidism, idiopathic hypercalciuria, and some of the frontiers of research and of speculation in all of these areas. The subject matter is diverse because kidney stones themselves are diverse in composition and in pathogenesis. More than 50 years ago Howard Kelly wrote presciently, "No stretch of chemical or physical imagination will permit so heterogeneous a group of compounds (as renal stones) to be ascribed to a common origin, or their disposition in kidney, ureter, or bladder to be uniformly charged to an identical cause."[4] Pursuit of this heterogeneity enlivens all current research in this important medical problem.

Montaigne, who suffered much from kidney stones, wrote as follows: "I feel everywhere men tormented with same Disease; and am honour'd by the Fellowship, forasmuch as Men of the Best Quality are most frequently afflicted with it; 'tis a noble and dignified Disease. And were it not a good office to a man to put him in mind of his end? My kidneys claw me to purpose." Stones still too frequently claw our kidneys, but the new insights of conduit chemistry offer hope that this ancient malady can be both understood and arrested. Perhaps then we can truly and finally emerge from the Stone Age.

LLOYD H. SMITH, Jr, MD

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Physicians and Animal Experimentation

ANIMAL EXPERIMENTATION has been vital in the development of the first polio vaccine, the isolation and use of insulin, the discovery of a vaccine for canine parvovirus (which causes a lethal infection in dogs), the production of antibiotics to treat pathologic microbes, research to improve cancer treatment, and the search for therapy against human immunodeficiency virus disease.[1] It is estimated that 17 to 22 million laboratory animals are used and killed each year, of which 90% are rodents and 1% to 2% are dogs and cats (150,000 to 200,000 animals).[2] To ensure appropriate and humane care of experimental animals, protective legislation was passed in the Animal Welfare Act of 1966 in the United States. In the 1970s and 1980s, a strong animal rights movement evolved in the United States intent on protecting animals and, in many cases, proposing that animals should have the same rights as human beings. For example, People for the Ethical Treatment of Animals state, "There is no rational basis for separating out the human animal. A rat is a pig is a dog is a boy. They're all animals."[3] Biomedical scientists and others are currently alarmed by the potential of the animal rights movement to convince the public to support and possibly pass restrictive legislation that would substantially decrease the ability of modern medical science to use animals in experiments.[4]

In this issue of the journal, Gelpi calmly and thoughtfully points out that there are two sides to the issue of animal experimentation and that physicians should educate themselves and become involved in this controversy.[5] Gelpi proposes that physicians as moderates "may be able to bring both sides of the animal rights controversy together in a spirit of mutual tolerance and in the common cause of promoting both human and animal welfare." This is a noble ideal and certainly worth the attention of physicians because extremism on either side is not acceptable.

Pardes and co-workers in their recent article on physicians and the animal rights movement underscored the extreme position of many of the animal rights organizations and called for clinicians to recognize the need for animal studies in the life sciences and to take responsibility for opposing what Woolsey called "the domination of knowledge by ignorance."[4,6] They pointed out that most health scientists are responsible and care for animals in a professional way. They called for vigilance in ensuring that scientists comply with regulations and that institutional review committees on animal research continue to do a careful job.

There is no question there have been examples of scientists and institutions who have not done a good job in caring for experimental animals in a humane way. In addition, it is questionable whether low-quality, duplicative, or mediocre research that results in the death of many animals should continue to be done.

The moral status of animals is at the basis of the disagreement between members of the animal rights movement and persons who support continued animal experimentation.[7] There is a moderate position that ascribes great moral worth to animals but allows them to be used for research under certain conditions.[1] This view is based on the principle of humane treatment, which obligates persons to use animals for research only when absolutely necessary and to minimize any suffering incurred by research. Investigators who believe they must use animals in their experiments should always ask

four important questions[1]: Have I sought for or tried to develop methods that obviate the use of animals? Am I proposing to use an appropriate species of animal? Does my protocol project using the fewest possible number of animals? Is my proposed use of animals in accord with the principle of humane treatment?

Great controversy arose after various examples of inappropriate human experimentation were identified in the 1960s. Experiments were often done on human subjects without informed consent, and some of the experimental designs were blatantly unethical. This led to the development in 1974 of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. Perhaps it is time for the federal government to appoint a commission to examine the use of animals in experiments and to analyze the different points of view concerning animal rights and morality. The appointment of a national commission for the protection of animal subjects in biomedical research would help all Americans understand the issues and establish reasonable guidelines for animal experimentation.

Animals should be used in experiments only when clearly necessary, and they should always be treated according to the principle of humane treatment. A dog is not a boy but still can be a loving companion and friend. Animals have feelings, and their lives have value. Extreme acts carried out by elements of the animal rights movement and inappropriate animal experimentation should stop. As Gelpi recommends, physicians should become more knowledgeable concerning animal experimentation and the animal rights movement so that they can assist in solving this problem. A moderate position can be identified, and the creation of a national commission for the protection of animal subjects in biomedical research might assist in the process.

THOMAS A RAFFIN, MD
Associate Professor and Chief
Division of Pulmonary and Critical Care Medicine
Stanford University Medical Center
Co-Director
Stanford University Center for Biomedical Ethics
Stanford, California

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International Health

THE BIGGEST HEALTH CARE breakthrough of this century, affecting the lives of millions throughout the world, occurred in 1978 at a historical meeting, convened by the World Health Organization (WHO) at Alma-Ata in the USSR.[1] This revolution has embraced all the nations of the world at grassroots, community, and administrative levels, yet has bypassed North America and Europe. A set of unique health principles and an achievable goal of equity in health expressed as WHO's goal of health for all by the year 2000 became the priority of the 166 member nations. The target was the "global human being" in need of health—physical, mental, social, and spiritual—to reach his or her true potential without hindrance.

What is international health? There is no clear-cut definition, but to the novice it conjures a picture of health teams traveling from North America and Europe to the Third World, loaded with medical supplies and cures with the application of the latest antimicrobics, vaccines, and other technology. The top-down approach still looms in the minds of many. But the goals and ideals of WHO and, indeed, of most Americans, are to target the health care of the global human being. Hence, international health can best be described as "health care that is *shared* between nations (international) and encompasses multiple disciplines and sciences including Primary Health Care, Public Health Care, Nutrition, Maternal-Child and Women's Health, Geographic and Tropical Medicine, Infectious Diseases, and so on. Unlike the component disciplines, it has a *moral* and *spiritual* component."[2] This is in keeping with the idea of health as defined by the World Health Organization's charter. The principles and imperatives of "health for all"[1] include the following:

It is intended to reach everybody, particularly those in greatest need; it is intended to reach to the home and family level and not to be limited to health facilities; it is intended to involve a continuing relationship with persons and families. Primary health care is the key to health for all and should include the following concepts:

- Universal coverage of the population with care provided according to need—that is, equity, no matter how poor or remote.
- Services should be promotive, preventive, and rehabilitative.
- Communities should be involved in the development of services to promote self-reliance and reduce dependence.
- Approaches to health should relate to other sectors of development.

It is necessary to impress on the minds of our colleagues, especially those who are entering the field of international health, that sharing and moral and spiritual components are crucial elements in our bonding efforts abroad and at home and especially if we are going to usher in a "new world order." This leads to my addressing another quiet revolution that has just taken place in the past few months—the formation of a consortium for international health programs in North American medical schools.[2] This idea germinated in the minds of Lynn Bickley, MD, (University of Rochester, New York) and me and was presented to the business and planning committee meetings of the National Council of International Health in June 1990. The idea got momentum with the involvement of Hakon Torjesen (Case Western Reserve University School of Medicine, Cleveland, Ohio), Ron Pust, MD, and Ms Susan Moher (University of Arizona, Tucson), leading to the first meeting. All told, 34 academicians from 24 US Medical Schools attended the meeting at Tucson, Arizona. The movement is historically significant. It will bring together under one organization all of the diverse international activities of all American medical schools. All the schools are, however, free to pursue the genius of their own individual programs. The organization will have leverage at national and international levels in policymaking and in devising curricula. It will also address long-felt predoc-

toral, doctoral, and postdoctoral needs in international health with regard to clinical sites, funding issues, curricular changes, academic credits, career tracks, resource sharing, providing a "clearinghouse." This has been a dream of the American Medical Students Association —800 of its members have an active interest in international health (L. Barthauer, oral communication, February 1991).

One of the ways we can achieve good global health is for the consortium to help expand the medical schools' horizons. Currently they function primarily as educators and researchers and entities isolated from societal concerns. It is hoped that they will eventually become active collaborators with the WHO, providing moral, spiritual, and social leadership in bringing health to that global human being abroad and at home. It is a way of delivering the promise of health for all[3] in an equitable, caring, sensitive manner and training foreign and local health care workers to take on the incredible challenge that lies ahead. To quote from a recent elegant and succinct editorial, "The basic issue is not health or illness care. The basic issue precedes the point at which this care must intervene . . . . We must now pull together, clarify our values, reassert that vulnerable people are a high priority [all over the world], and move ahead."[4]

ANVAR VELJI, MD
Associate Clinical Professor
University of California, Davis, Medical Center
Chief, Infectious Disease
Kaiser Permanente Medical Center
Sacramento, California

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Lessons From the Practice

Desperately Seeking Primary Prevention

EDITOR'S NOTE: *To protect the privacy of the patient, the names and the location of the patient and the physician who wrote the Lesson will remain anonymous. No reprints are available.*

Christina came to see me on a Friday, 30 minutes before the office was to close. She was the last patient of the week.

She appeared pale, serious, and quiet. "I stuck myself with a needle. The patient had AIDS [acquired immunodeficiency syndrome]. He died this morning."

When did this happen?

"Last night, around midnight."

Have you seen anyone yet?

"No. I couldn't believe it had happened. I was busy taking care of the patient, who was really sick. When I finished my shift, I was exhausted, and I went home."

Christina and I discussed what had happened and why. As has become sadly routine, I gave her statistics: "Since the patient had AIDS, you have a 1-in-200 chance of becoming infected with HIV [human immunodeficiency virus]. Probably much less, since this was such a minor stick." And the protocol. "We should draw a baseline blood test for the virus and recheck at six weeks, three months, and six months."

She had completed her hepatitis B vaccination four months previously, and blood tests had revealed that she was now immune to hepatitis B, so this was not a concern. She had received tetanus toxoid two years previously after a needle-stick accident, so this was up to date.

We discussed the possibility of starting a regimen of zidovudine, or AZT, which sometimes is used in cases like this, although the benefit is unproven. Would she consider its use?

"No," she said. She had taken care of patients who received AZT and didn't care for its side effects. Christina was certain that she would not take AZT and that she would have been seen even sooner if she had been willing to do so.

We reviewed the confidential system of testing and her need for safe sexual practices. I provided routine postexposure counseling.

"If you are anxious or have any problem in the coming weeks, call me."

In our Employee Health Center, we see 10 to 15 employees with needle-stick injuries every month. I always feel concerned about these accidents, especially when the source is HIV-positive; I felt particularly concerned about Christina. Maybe it was because the patient who had AIDS was so sick and had died the next day. That weekend, Christina was very much on my mind.

Ten days later she called. "I have a sore throat and feel achy all over. I'm nauseous, too. Probably just the flu, right?"

It *was* flu season. "Chances are, yes," I said. She called back two days later.

"I'm having fevers to 102°, chills, and vomiting. I feel like I was hit by a truck. I have no appetite and can't sleep, and my glands are swollen. I'm really feeling scared." The baseline HIV test from her previous visit had returned "nonreactive," or negative. She came in to see me that day, and her examination was normal, including a complete blood cell count. She seemed reassured. Three days later, when she continued to have fevers, malaise, and achiness, she returned to see me. We repeated the HIV test.

I felt worried and wondered if I should have insisted on her taking AZT. I did not share my deep concerns with my patient, whose chances of contracting an infection from her exposure were so small.

A week later Christina was feeling better. Her repeat HIV test was returned "nonreactive." We spoke by phone. "I think it was the flu," she said. "It took a week for me to begin to feel better."

Three weeks later, again on a Friday afternoon, the nurse practitioner asked me into her office. "Look at this," she said.

She showed me a laboratory result, encoded with a number instead of a name, as is done in the Employee Health Center to ensure confidentiality with employee HIV results. I decoded the sample. The number belonged to Christina—her six-week routine follow-up blood test for HIV antibodies was positive. She was infected.

Unbelievable. I shook my head. Couldn't be. I cried, knowing it was probably true. I would repeat the test. But inside I knew that her fevers had been part of her acute retroviral illness and that she had seroconverted. How would I possibly be able to tell her? How would she manage? I kept shaking my head, wanting to change what had happened.

Again, all weekend I thought about Christina. Saturday night I dreamed of AIDS-infected needles piercing my legs.

I wanted to talk with Christina at a time when support services would be available, so Monday morning I called her at home. "I'd like to see you." She didn't ask why. Now, concern and fear registered in her voice. She came sharply at noon and brought along a close friend.

Her first reaction was profound sadness. "I had a feeling about this. This never should have happened," she said as she cried.

How many times has Christina gone over every moment of that night when she cared for that unnamed patient—and that one horrible moment when the needle stuck her left index finger? Such a tiny stick; she hardly felt it. But enough virus at the tip of that needle to infect her. Change her life. Puncture it. Her life forever altered by the tiny segment of protein now encoded in her cells.

The needle had been used by an intern to obtain blood for blood gas values and was left on the patient's bedstand, hid-

(Desperately seeking primary prevention. West J Med 1991 Sep; 155:310-311)

den from view. He was busy and didn't see the needle from his unsuccessful stick left enclosed between two Betadine-soaked gauze pads. Neither did Christina, as she was cleaning up. "I'm really sorry," he had said when he saw her get stuck. The intern still does not know the consequences of that moment of unintended carelessness. He has moved on to residency elsewhere. He cannot be told what happened without risking Christina's confidentiality.

The burden of secrecy weighed heavily on me. I felt like announcing to the entire medical center what had happened. I wanted to tell of the dangers. We must prevent such incidents from happening! But the need to protect Christina's identity prevented me. I identify with her, and her own burden, and at times feel incredible, undirected anger.

This has been a most difficult year for Christina. Last week she said to me, "I feel devastated. It's not getting easier."

I feel privileged to know Christina and admire her strength and courage. I wonder how one deals with an experience wrought with such fear. It will continue to affect her life. For the present, we continue to work together on preventing and following up on needle-stick exposures in our medical center.

* * *

"Lessons From the Practice" presents a personal experience of practicing physicians, residents, and medical students that made a lasting impression on the author. These pieces will speak to the art of medicine and to the primary goals of medical practice—to heal and to care for others. Physicians interested in contributing to the series are encouraged to submit their "lessons" to the series' editors.

JONATHAN E. RODNICK, MD
STEPHEN J. McPHEE, MD
Series' Editors

Poem

THE TORONTO DOGS

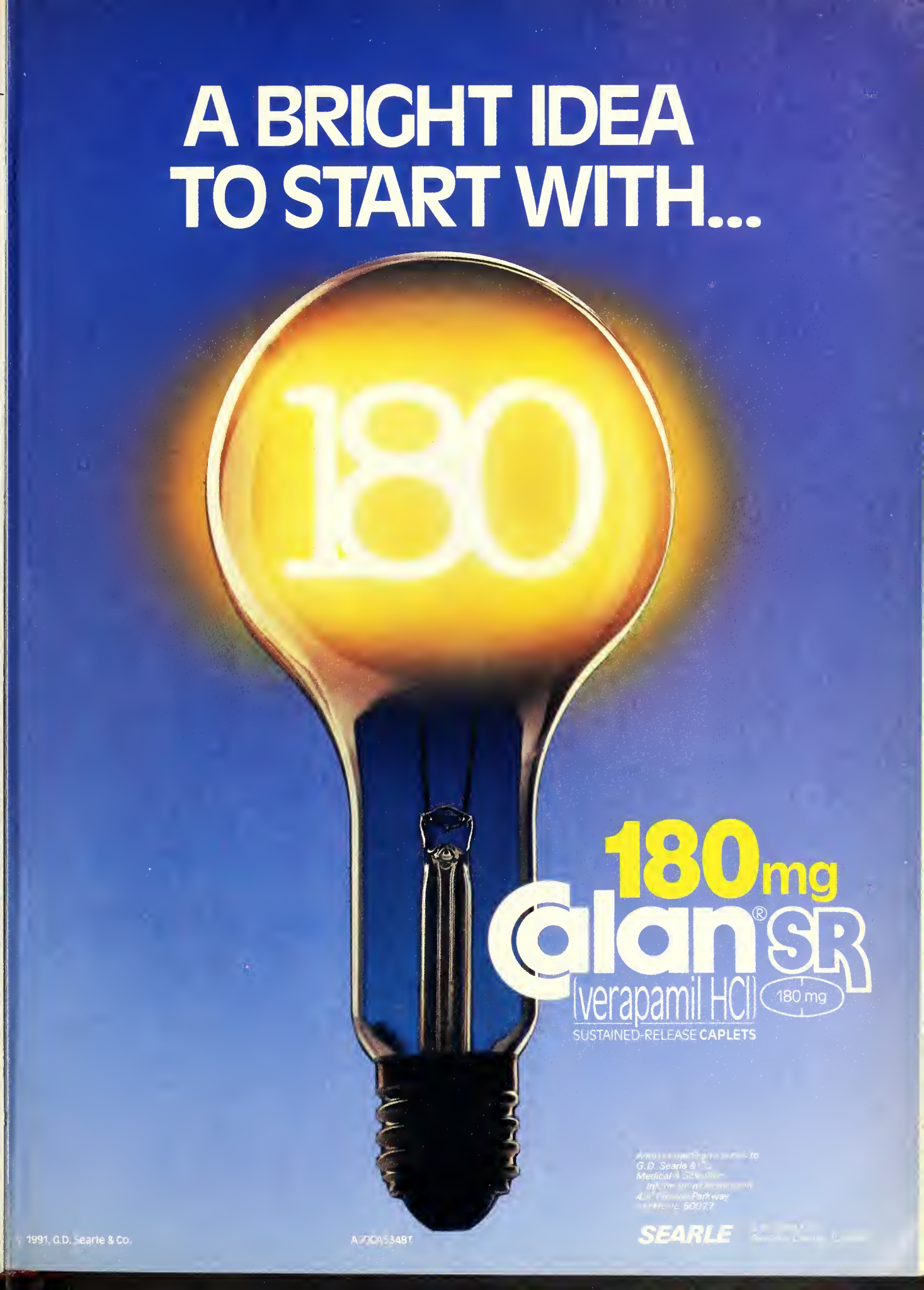
They looked at him with their soft eyes,
Only one question there.
One after the next they died, complaining not,
Their lives the paving stones of a long road
Whose end was only a dream in doctors' minds.
The road had started early, as all roads do,
The threshold an old cage in von Minkovski's lab
Where a lab boy, obscure to all,
Obscure as all those nameless dogs,
Had found a swarm of flies in the dry urine,
Sweet to taste if not to limbs.

In the hospitals and beds around the world
Young children died unconscious,
Their sugared blood unburned,
Their limbs tabetic and their eyes all spent in hope.

The furry friends in metal cages
Lay in softness unprotesting
And told those Torontonians under shadows of the night
"Go on, don't mind us, we're trying too!"

One day at last, as if a miracle of sheer persistence
Performed before those altars with no church,
The quiet juices coming of the entrails of those quiet dogs,
Like tears of angels became crystals in a tube,
And children the world over
Lived to tell their children
Of the dreams they dreamt
And at the end of that old road
So paved with silent dolor
A spark of dogness lit the skies of God.

CARLOS A. SCHAFFENBURG, MD©
Chevy Chase, Maryland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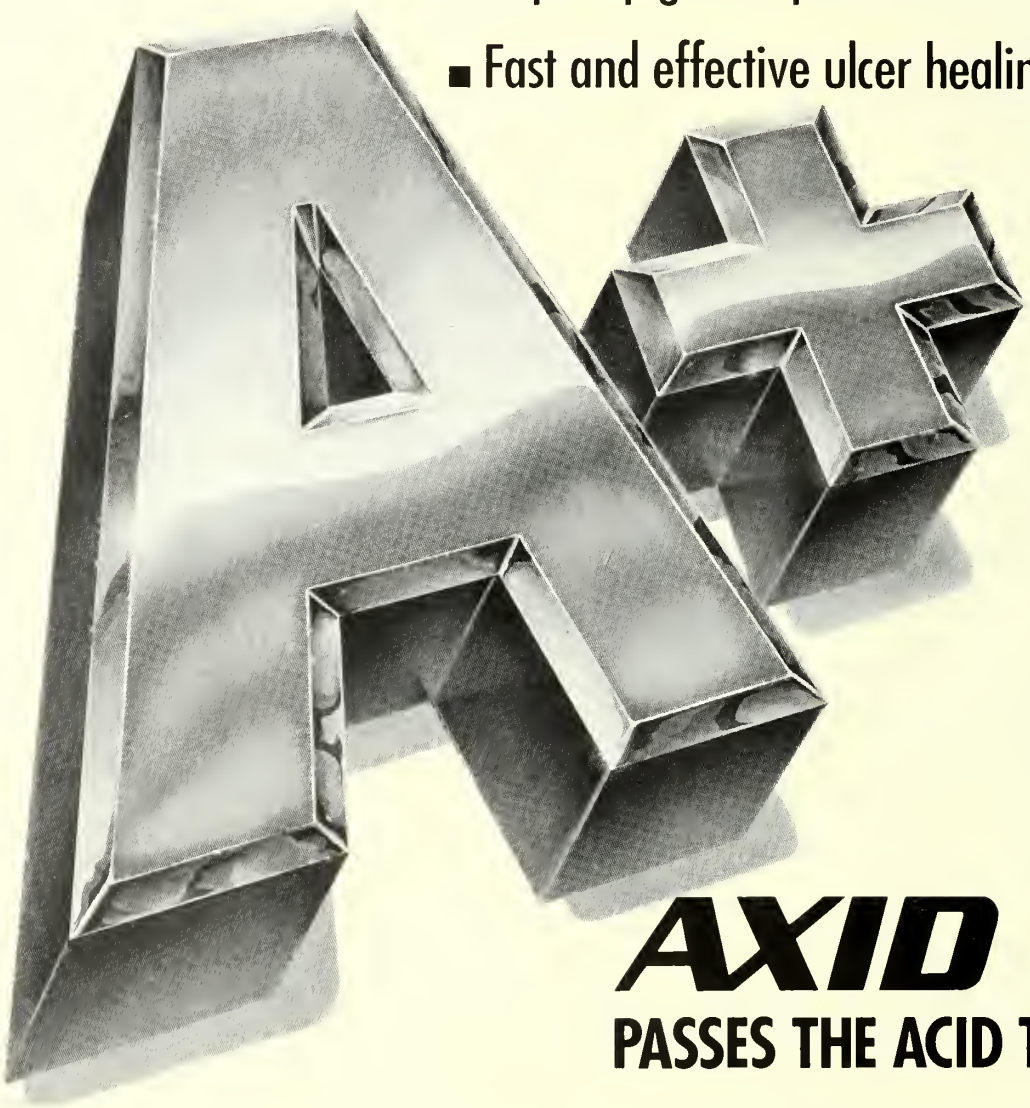

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2. *Maintenance therapy*—for healed duodenal ulcer patients at a reduced dosage of 150 mg h.s. The consequences of therapy with Axid for longer than 1 year are not known.

Contraindications: Known hypersensitivity to the drug. Because cross sensitivity in this class of compounds has been observed, H_2-receptor antagonists, including Axid, should not be administered to patients with a history of hypersensitivity to other H_2-receptor antagonists.

Precautions: *General*—1. Symptomatic response to nizatidine therapy does not preclude the presence of gastric malignancy.

2. Dosage should be reduced in patients with moderate to severe renal insufficiency.

3. In patients with normal renal function and uncomplicated hepatic dysfunction, the disposition of nizatidine is similar to that in normal subjects.

Laboratory Tests—False-positive tests for urobilinogen with Multistix® may occur during therapy.

Drug Interactions—No interactions have been observed with theophylline, chlordiazepoxide, lorazepam, lidocaine, phenytoin, and warfarin. Axid does not inhibit the cytochrome P-450 enzyme system, therefore, drug interactions mediated by inhibition of hepatic metabolism are not expected to occur. In patients given very high doses (3,900 mg) of aspirin daily, increased serum salicylate levels were seen when nizatidine, 150 mg b.i.d., was administered concurrently.

Carcinogenesis, Mutagenesis, Impairment of Fertility—A 2-year oral carcinogenicity study in rats with doses as high as 500 mg/kg/day (about 80 times the recommended daily therapeutic dose) showed no evidence of a carcinogenic effect. There was a dose-related increase in the density of enterochromaffin-like (ECL) cells in the gastric oxyntic mucosa. In a 2-year study in mice, there was no evidence of a carcinogenic effect in male mice, although hyperplastic nodules of the liver were increased in the high-dose males as compared with placebo. Female mice given the high dose of Axid (2,000 mg/kg/day, about 330 times the human dose) showed marginally statistically significant increases in hepatic carcinoma and hepatic nodular hyperplasia with no numerical increase seen in any of the other dose groups. The rate of hepatic carcinoma in the high-dose animals was within the historical control limits seen for the strain of mice used. The female mice were given a dose larger than the maximum tolerated dose, as indicated by excessive (30%) weight decrement as compared with concurrent controls and evidence of mild liver injury (transaminase elevations). The occurrence of a marginal finding at high dose only in animals given an excessive and somewhat hepatotoxic dose, with no evidence of a carcinogenic effect in rats, male mice, and female mice (given up to 360 mg/kg/day, about 60 times the human dose), and a negative mutagenicity battery are not considered evidence of a carcinogenic potential for Axid.

Axid was not mutagenic in a battery of tests performed to evaluate its potential genetic toxicity, including bacterial mutation tests, unscheduled DNA synthesis, sister chromatid exchange, mouse lymphoma assay, chromosome aberration tests, and a micronucleus test.

In a 2-generation, perinatal and postnatal fertility study in rats, doses of nizatidine up to 650 mg/kg/day produced no adverse effects on the reproductive performance of parental animals or their progeny.

Pregnancy—Teratogenic Effects—Pregnancy Category C—Oral reproduction studies in rats at doses up to 300 times the human dose and in Dutch Belted rabbits at doses up to 55 times the human dose revealed no evidence of impaired fertility or teratogenic effect; but, at a dose equivalent to 300 times the human dose, treated rabbits had abortions, decreased number of live fetuses, and depressed fetal weights. On intravenous administration to pregnant New Zealand White rabbits, nizatidine at 20 mg/kg produced cardiac enlargement, coarctation of the aortic arch, and cutaneous edema in 1 fetus, and at 50 mg/kg, it produced ventricular anomaly, distended abdomen, spina bifida, hydrocephaly, and enlarged heart in 1 fetus. There are, however, no adequate and well-controlled studies in pregnant women. It is also not known whether nizatidine can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Nizatidine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers—Studies in lactating women have shown that 0.1% of an oral dose is secreted in human milk in proportion to plasma concentrations. Because of growth depression in pups reared by treated lactating rats, a decision should be made whether to discontinue nursing or the drug, taking into account the importance of the drug to the mother.

Pediatric Use—Safety and effectiveness in children have not been established.

Use in Elderly Patients—Healing rates in elderly patients were similar to those in younger age groups as were the rates of adverse events and laboratory test abnormalities. Age alone may not be an important factor in the disposition of nizatidine. Elderly patients may have reduced renal function.

Adverse Reactions: Clinical trials of varying durations included almost 5,000 patients. Among the more common adverse events in domestic placebo-controlled trials of over 1,900 nizatidine patients and over 1,300 on placebo, sweating (1% vs 0.2%), urticaria (0.5% vs <0.01%), and somnolence (2.4% vs 1.3%) were significantly more common with nizatidine. It was not possible to determine whether a variety of less common events were due to the drug.

Hepatic—Hepatocellular injury (elevated liver enzyme tests or alkaline phosphatase) possibly or probably related to nizatidine occurred in some patients. In some cases, there was marked elevation (>500 IU/L) in SGOT or SGPT and, in a single instance, SGPT was >2,000 IU/L. The incidence of elevated liver enzymes overall and elevations of up to 3 times the upper limit of normal, however, did not significantly differ from that in placebo patients. All abnormalities were reversible after discontinuation of Axid. Since market introduction, hepatitis and jaundice have been reported. Rare cases of cholestatic or mixed hepatocellular and cholestatic injury with jaundice have been reported with reversal of the abnormalities after discontinuation of Axid.

Cardiovascular—In clinical pharmacology studies, short episodes of asymptomatic ventricular tachycardia occurred in 2 individuals administered Axid and in 3 untreated subjects.

CNS—Rare cases of reversible mental confusion have been reported.

Endocrine—Clinical pharmacology studies and controlled clinical trials showed no evidence of antiandrogenic activity due to nizatidine. Impotence and decreased libido were reported with equal frequency by patients on nizatidine and those on placebo. Gynecomastia has been reported rarely.

Hematologic—Fatal thrombocytopenia was reported in a patient treated with nizatidine and another H_2-receptor antagonist. This patient had previously experienced thrombocytopenia while taking other drugs. Rare cases of thrombocytopenic purpura have been reported.

Integumental—Sweating and urticaria were reported significantly more frequently in nizatidine- than in placebo-treated patients. Rash and exfoliative dermatitis were also reported.

Hypersensitivity—As with other H_2-receptor antagonists, rare cases of anaphylaxis following nizatidine administration have been reported. Rare episodes of hypersensitivity reactions (eg, bronchospasm, laryngeal edema, rash, and eosinophilia) have been reported.

Other—Hyperuricemia unassociated with gout or nephrolithiasis was reported. Eosinophilia, fever, and nausea related to nizatidine have been reported.

Overdosage: Overdoses of Axid have been reported rarely. If overdosage occurs, activated charcoal, emesis, or lavage should be considered along with clinical monitoring and supportive therapy. Renal dialysis does not substantially increase clearance of nizatidine due to its large volume of distribution.

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References

1. Data on file, Lilly Research Laboratories.
2. *Scand J Gastroenterol* 1987;22(suppl 136):61-70.
3. *Scand J Gastroenterol* 1987;22(suppl 136):47-55.
4. *Am J Gastroenterol* 1989;84:769-774.

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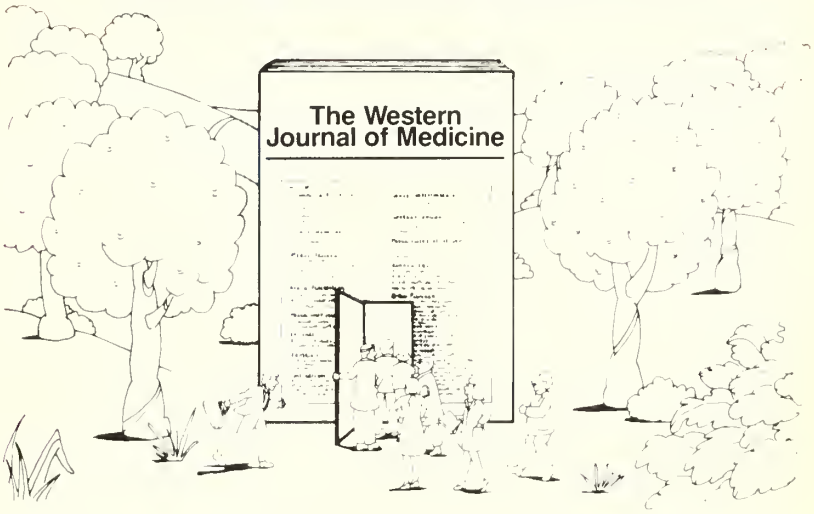

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(Continued on Page 318)

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NORTHERN CALIFORNIA. Seeking qualified Pediatricians (PL-3 and higher) for part-time positions in all departments of Kaiser Permanente Medical Center. Also seeking second in-house Pediatrician with Emergency, Critical Care or Neonatal experience (12 and 24 hour shifts available). Please call or send CV to Gabriel J. Escobar, MD, Department of Pediatrics, Kaiser Permanente, 1425 S. Main St, Walnut Creek, CA 94596; (415) 295-5169. EOE.

BC/BE FAMILY PRACTITIONER AND GENERAL INTERNIST needed to fill positions at our busy multispecialty clinic in north Seattle. This modern clinic is extremely well run, well equipped with many ancillary services and is located within three miles of a 240-bed hospital. Opportunity available to do some teaching with local residency program. Diverse patient population includes fee-for-service, managed care, and some retired military. Year-round outdoor recreation includes numerous lakes, rivers, national parks, mountains, and Puget Sound. Competitive salary and excellent benefits. Contact Mary Anderson, Pacific Medical Center, 1200 12th Ave S., Seattle, WA 98144; (206) 326-4100.

PHYSICIAN OPENING. Ambulatory care/minor emergency center. Full-/part-time for Family Practice/Internal Medicine/Emergency Medicine trained, experienced physician located in Tacoma area. Flexible scheduling, pleasant setting, quality medicine. Contact David R. Kennel, MD, 5900 100th St SW, Ste 31, Tacoma, WA 98499; (206) 584-3023 or 582-2542.

BC/BE DIAGNOSTIC RADIOLOGIST needed immediately for small two person rural office and hospital practice in northeastern Oregon. X-ray, ultrasound, nuclear medicine, CT, mammo, with mobile MRI in the works. Contact Beverly Jahncke; (503) 276-2431.

SEATTLE/FACTORIA. An excellent opportunity exists for a three quarter to full-time BE/BC Family Practitioner to join the rapidly growing Providence Medical Care Center in Bellevue. This is an attractive, four-year-old facility in the high growth Factoria area. The center is located at the I-405/I-90 Interchange making it convenient for patients traveling from Seattle, Bellevue, Issaquah, and Renton. The practice provides Family Medicine, Internal Medicine, Orthopedics, Cardiology, and Hematology services. The ideal candidate will practice the full spectrum of Family Medicine, including Obstetrics. An incentive compensation package with a guaranteed base and benefits is being offered. Seattle is known as a beautiful area with many cultural events and recreational opportunities. The Medical Care Center is affiliated with Providence Medical Center, a 370 plus-bed teaching hospital in Seattle, Washington. For more information contact Sandra Kozlowski, Providence Medical Center, 500 17th Ave C-34008, Seattle, WA 98124; (206) 320-2039.

PHYSICIANS WANTED

NORTHERN CALIFORNIA

San Jose's leading multispecialty group is growing. We are seeking BE/BC physicians in the following specialties:

- Urgent Care
- Internal Medicine/GI
- Internal Medicine/General
- Physiatry
- Occupational Medicine
- Family Practice
- OB/GYN

If you are committed to excellence and strongly motivated for success, we would like to hear from you. Please send your CV to Maureen Forrester, San Jose Medical Group, Inc, 45 S 17th St, San Jose, CA 95112; **or call (408) 282-7833.**

BE/BC UROLOGIST to join busy 28 doctor multispecialty group practice. Excellent practice opportunity, full range of benefits, early partnership status. For more information contact Shane Spray, 1400 Kincaid, Mount Vernon, WA 98273; (206) 428-2524.

GENERAL SURGEON. Full-time BC/BE General Surgeon for multispecialty group in southeast Los Angeles. Office/hospital and consulting practice. Spanish a plus. Top salary, benefits, and malpractice insurance. Potential for shareholdership second year. Send CV to Craig Kaner, Administrator, All Care Medical Group, Inc., 2675 E. Slauson Ave, Huntington Park, CA 90255; (213) 589-6681.

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(Continued on Page 322)

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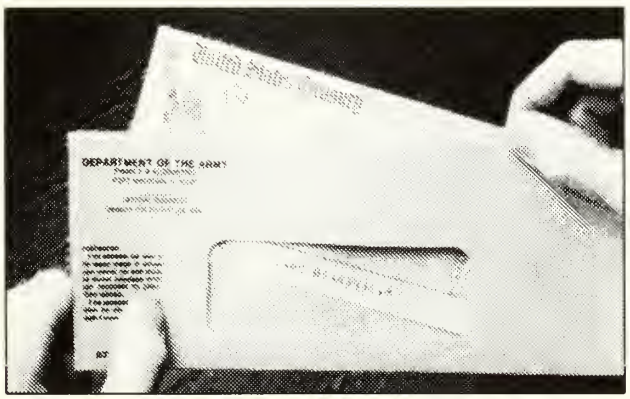

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(Continued from Page 320)

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- Excellent call and coverage support
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- Guaranteed salaries
- Comprehensive benefits packages and pension plans
- Paid malpractice insurance
- Abundant and affordable housing
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Become part of the tradition. **Call Tim Skinner, Manager, Physician Recruitment, COLLECT at 1-608-782-7300.** Or send your CV to him: **Gundersen Clinic, Ltd. 1836 South Avenue, Dept. W-7, La Crosse, WI 54601.** An equal opportunity employer.

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ACTIVE TWO PERSON FAMILY PRACTICE seeking third partner. Full spectrum care with excellent hospital and specialist support. Local schools are excellent in this beautiful waterfront community adjacent to the San Juan Islands, Mt. Baker, fishing, skiing, and sailing. One hour from Seattle or Vancouver, B.C. Contact Mike James, MD; (206) 293-6642.

OTOLARYNGOLOGIST. BC/BE to join 28 physician multispecialty group practice. Located in beautiful Pacific northwest between Seattle and Vancouver, BC. Contact Shane Spray, 1400 E. Kincaid, Mount Vernon, WA 98273.

PRIMARY CARE PHYSICIAN wanted for expanding eastern Washington clinic. Full- and part-time positions available. Located in prime recreational area. Skiing, sailing, fishing, hunting all within a short distance. Enjoy mild climate, excellent schools and a major university branch campus in growing community of 100,000 plus. Challenging work in a superbly equipped clinic with state-of-the-art lab, x-ray, laser, and endoscopy. Above average compensation and benefits including malpractice, health insurance, and CME. Contact Dr Stephen L. Smith, 310 Torbett, Richland, WA 99352; (509) 545-8340 or FAX (509) 545-1136.

EMERGENCY MEDICINE. Emergency Medicine group seeking career oriented ACLS, ATLS certified physician for an immediate opening. Moderate volume; income $140,000 plus. Great outdoor activities including hunting, fishing, boating, skiing, sailing, camping, and hiking in south central Washington on the Columbia River. Send CV to Kennewick Emergency Physicians, PS, PO Box 6192, Kennewick, WA 99336-6192; or call (509) 627-1798.

(Continued on Page 323)

PHYSICIANS WANTED

PHYSICIAN OPPORTUNITIES NATIONWIDE
For all specialities for hospitals, clinics, multispecialty groups, partnership and solos. Contact Jim Grant in complete confidence at the bay area specialists. **G & G Physician Services, 1400 Coleman, Ste B-22, Santa Clara, CA 95050; or call (800) 727-2478, FAX # (408) 727-7390.** Never a fee to the physician.

SAN JOAQUIN VALLEY. Excellent opportunity for Family Practitioner to serve the underserved. No night call or weekends. Competitive salary plus benefits, paid malpractice. Agricultural community, one hour from the mountains, two hours from the coast. Bilingual English-Spanish helpful. Send CV to Hugh F. Stallworth, MD, Fresno County Department of Health, PO Box 11867, Fresno, CA 93775; (209) 445-3202.

BC/BE FAMILY PRACTITIONER, OB-competent, for nonprofit community clinic in California redwood country. Rural but sophisticated university town. Contact Donald Verwayen, Northcountry Clinic, 785 18th St, Arcata, CA 95521; (707) 822-2481.

INTERNIST. Immediate opening. Large, established, rapidly growing Los Angeles medical facility. High salary. Full benefits. Malpractice insurance paid. Contact Mr Miller; (213) 384-2504.

FAMILY PRACTICE PHYSICIAN. Full-time in a busy walk-in medical clinic. Located in Visalia, California (Tulare County). Malpractice insurance, good salary, etc. Please call (209) 627-5555 for more information.

ASSOCIATE IN PEDIATRICS. Kern Medical Center, Bakersfield, California, a teaching hospital affiliated with UCLA and UCI Schools of Medicine, seeks an Associate in the Division of Pediatrics. Prerequisites include eligibility or certification by the American Board of Pediatrics, strong interest in teaching and qualifications for faculty appointment in UCLA Department of Pediatrics. Comprehensive salary and benefit package. A part-time private practice is permitted. Medical center is in central California, a mid-sized urban community with moderate cost of living. Send CV and inquiries to Navin Amin, MD, Chairman, Department of Family Practice/Pediatrics, Kern Medical Center, 1830 Flower St, Bakersfield, CA 93305.

NORTHERN CALIFORNIA GENERAL SURGEON. Opportunity for General Surgeon with thoracic and vascular experience. Salary leading to partnership. Surgical group in northern California rural community. Excellent quality of life. Reply to 1165 S Dora, Ste A-3, Ukiah, CA 95482; (707) 462-7579.

CARDIOLOGIST—BC/BE, invasive or noninvasive, to join busy practice in beautiful northern Utah college community. New cath lab. Complete echo/nuclear services. Send CV to Number 240, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

SEATTLE/TACOMA. Join highly successful 26 physician Primary Care group with reputation for quality care. Located within 1/2 hour of Seattle and Tacoma. Competitive salary plus benefits with partnership in two years. For more information, please contact Ken Baker, President, Physician Search Group, 120 Montgomery St, Ste 710, San Francisco, CA 94104; (415) 399-8840.

PHYSICIANS WANTED

INTERNIST BE/BC. Superior opportunity for Internist within a growing innovative group. Be a part of a progressive growing group providing care in the San Gabriel Valley. Competitive salary and full benefit package available to qualified candidate. Please send CV to Shirley Dykes, Arroyo Seco Medical Group, 800 S Fairmount Ave, Ste 110, Pasadena, CA 91105.

ORTHOPAEDIST—BC/BE for expanding San Francisco bay area practice emphasizing Occupational Medicine and medical-legal evaluation seeks full-time nonsurgery practicing Orthopaedist. Outstanding reputation, facilities and support staff, established referral base. Unique income opportunities. Submit CV and letter stating professional goals and availability to: Administrator, 2040 Polk St, Box 337, San Francisco, CA 94109.

BE/BC INTERNIST sought with or without subspecialty interest to replace departing partner in busy seven member Internal Medicine practice ten miles south of San Francisco. Contact Diane Davis, MD; (415) 583-5352, 1001 Sneath Ln, San Bruno, CA 94066.

FAMILY PRACTICE, BC/BE to join group practice in growing southwestern town. Full service clinic, 280-bed hospital. Offering competitive salary, equal call schedule, partnership. Contact Myrna Hughes, Arizona Western Medical Center, 2149 W. 24th St, Yuma, AZ 85364; (602) 344-1400.

PEDIATRICIAN, BC/BE to join group Family Practice/Pediatrics. Growing community with growing pediatric population. Active Nursery Level II hospital and nursery with NNP coverage. Offering competitive salary, equal call schedules, partnership. Contact Myrna Hughes, Arizona Western Medical Center, 2149 W. 24th St, Yuma, AZ 85364; (602) 344-1400.

MEMORIAL CLINIC offers excellent opportunity for BC/BE Family Practitioner to establish a second Family Practice neighborhood clinic. OB optional. Competitive salary and excellent benefits. Send CV to Memorial Clinic, Attention Inge Hart, 500 Lilly Rd, N.E., Olympia, WA 98506; (206) 456-1122, ext 249.

WASHINGTON. Openings for career oriented Emergency Physicians, BC in Emergency or Primary medical specialty. Seattle metropolitan hospital with 54,000 annual visits. Excellent salary in a stable growing group. Contact Dan Hiatt in care of Linda Johnson, 8009 S. 180th, Ste 110, Kent, WA 98032; (206) 575-2595.

MEDICAL DIRECTOR vacancy at Agnews Developmental Center, in San Jose. Qualification requirements are five years of clinical experience as a physician, working with developmentally or mentally disabled clients, or in state service one year as a Program Director (Medical) or two years as Program Assistant (Medical) or Program Review Consultant (Medical). Competitive salary and benefits. Contact Dr Karen Kral; (408) 432-8500, ext 2208, 3500 Zanker Rd, San Jose, CA 95134.

NORTHERN CALIFORNIA. Excellent opportunity in picturesque alpine community for (BC/BE) OB/GYN seeking slower paced lifestyle. Four season recreational area with mild temperature boasts skiing, boating, and hiking. Join six person Primary Care group and enjoy busy GYN practice and 100-plus deliveries per year. Comprehensive benefits offered with first year guarantee. Call Jan Jordan at (800) 462-1857.

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The County of Riverside Department of Health is seeking a hands-on Public Health Officer to plan, organize and direct a multitude of services within our Public Health Program.

You will consult with our staff and the medical profession on public health issues, evaluate/change existing programs and recommend new programs. You will also speak before professional/community groups, advise the public on health hazards/problems and oversee administrative functions.

Basic requirements include 4 years experience as a physician in a public health agency with a generalized program and at least 1 year in an administrative capacity. For information on additional requirements, please call Dave Wahlquist at: **714-275-3587.**

In addition to a competitive salary and comprehensive benefits, the County of Riverside offers an enjoyable lifestyle with close proximity to the beach and the mountains. Make a move for the better to one of Southern California's most dynamic and progressive counties. Send your resume/CV to: **County of Riverside, 4080 Lemon St., Room 109, Riverside, CA 92502-1569. EOE/AA**

(Continued from Page 322)

PHYSICIANS WANTED

GENERAL SURGEON to join two physician surgical practice offering full breadth of General Surgery with part-time a possibility. Emphasis on breast disease and access for dialysis. The opportunity is located in Spokane in the scenic Intermountain Northwest. Enjoy excellent outdoor recreation, good schools, quality lifestyle in an expanding economy. Submit CV to Number 247, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

CALIFORNIA. MEDICAL ONCOLOGIST/HEMATOLOGIST BC/BE needed urgently to join a busy practice in the San Francisco east bay area. Excellent opportunity with built-in referrals. Terms are attractive and negotiable, including early full partnership. Access to ECOG/NSABP protocols through C-COP. For immediate correspondence, FAX CV to (415) 778-3567 or call (415) 778-0679. Position available immediately.

NATIONWIDE TRAVEL. Health research organization seeks physician for National Health and Nutrition Examination Survey sponsored by the US Public Health Service. Individual will be part of a large medical team conducting health examinations in government mobile exam centers traveling to 88 areas of the US through 1993. Must be licensed in one state. One year minimum commitment and full-time continuous travel required. Competitive salary, paid malpractice, per diem, car, four weeks paid vacation per year, holidays, and health, life, dental, disability insurance offered. Call Beverly Geline, (800) 937-8281, ext 8248. Westat, Inc, Rockville, MD, EOE/M/F/V/H.

BEAUTIFUL OREGON COAST. Private multispecialty cooperative with excellent facility seeking Family Practice physician to join five full-time Family Practitioners. Full spectrum of Family Practice. In-house lab, x-ray, day surgery. Contact Marce Knight, 1900 Woodland Dr, Coos Bay, OR 97420; (503) 267-5151, ext 294 or (800) 234-1231.

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Excellent opportunity for BC/BE Internists interested in private or group practices. Cody, Wyoming, is located only 50 miles from Yellowstone National Park. This attractive community is abundant in fishing, hunting, and outdoor sports. NO STATE INCOME TAX! Facility consists of 46-bed Acute Care, 107-bed attached Long Term Care Center and 20-bed Chemical Dependency Center. For more information call:

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West Park Hospital

ORTHOPEDIC SURGEONS. Orthopedic Surgeon for busy Orthopedic service in 223-bed teaching hospital with residencies in General Surgery, Internal Medicine, OB/GYN, and Family Practice. Should be BC/BE. Experience in Arthroscopy preferred. Salary and compensation plan negotiable depending on experience. Hospital located in beautiful northern San Joaquin valley close to major cities and skiing areas. Please submit CV and references or contact Nathaniel Matolo, MD, Chief of Surgery, San Joaquin General Hospital, PO Box 1020, Stockton, CA 95201; (209) 468-6600. AA/EOE.

INTERNIST/FAMILY PRACTITIONER—Northern California. Immediate opportunity for BC/BE Internal Medicine/Family Practice. Practice associate emphasized or solo practice. Located north of San Francisco in wine country with outdoor activities. Assistance available for relocation and establishment of practice. Contact Margaret Ward, Redbud Community Hospital, Box 6720, Clearlake, CA 95422; (707) 994-6486.

REDWOOD COAST. Primary Physician for community health center providing quality care to low income population. Excellent hospitals, support services. Supervise midlevels. Unequaled life-style combines spectacular beaches and redwoods with amenities of university town. Federal loan repayment program. Contact M. Sterling, HODC, 770 10th, Arcata, CA 95521; (707) 822-2957.

SAN FRANCISCO BAY AREA. Desire BC/BE Family Practitioner for small, rapidly growing outpatient Family Practice. Flexible hours. Warm, supportive environment. Competitive compensation/benefits. Contact Steven Kaplan, MD, 3585 Clayton Rd, Concord, CA 94519; (415) 798-1500.

CHEYENNE, WYOMING. Immediate opening available for a dedicated, career oriented, full-time physician with Urgent Care facility in Cheyenne, Wyoming. Competitive compensation plus malpractice insurance. Approximately 14 days per month, standard 12 hour shifts. Excellent living conditions, high quality school system, moderate taxes and living expenses, exciting recreational opportunities in the heart of the Rocky Mountain region. Call now for additional information or send CV to Janet Cowley, Recruitment Coordinator, PO Box 805, Cheyenne, WY 82003; call toll-free, (800) 877-1436, or (307) 632-1436, FAX (307) 635-4642.

(Continued on Page 324)

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OB/GYN—Southern California. Career opportunities for ambitious Obstetricians desiring private practice. Growing, prestigious, university-affiliated south bay medical center is recruiting BC/BE Physicians for expanding solo and group practices. Excellent compensation. Submit CV to J. Michaels, 2600 Cliff Dr, Newport Beach, CA 92663.

SMALL GROUP OF FAMILY PHYSICIANS seeks a fourth associate to practice in Culver City (located in west Los Angeles). Partnership after one year. No buy in. Salary, benefits. Call shared equally. Send CV to 10100 Culver Blvd, Culver City, CA 90230; or call Ms Foreman at (213) 837-5221.

INVASIVE CARDIOLOGIST. Beautiful Pacific northwest. Excellent opportunity. Quality care, heart institute setting. Please send current CV to Number 245, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

NEW MEXICO. Excellent opportunity for BC/BE OB/GYN, Internal Medicine, and Family Practice to join successful practices or start new in a growing community. Plan on full practice from the beginning. Enjoy sunshine, skiing, hiking, fishing, and hunting in a southwestern lifestyle. For further information on benefits and compensation contact Anne Winter, RN, Director of Professional Development, St Joseph Healthcare System, Albuquerque, NM; (505) 246-8003.

SOUTHERN CALIFORNIA. Busy, lucrative practice in thriving medical community. One hour from beaches and mountains. Senior physician is ready to enjoy the rewards of building this excellent practice. Prestigious 300-bed community hospital will assist in practice acquisition and new set up. For more information, please contact Ken Baker, President, Physician Search Group, 120 Montgomery St, Ste 710, San Francisco, CA 94104; (415) 399-8840.

Western States OPENINGS

Many multispecialty groups and hospitals have asked us to recruit for over 300 positions of various specialties. Both permanent and locum tenens. Send CV to **Western States Physician Services, 5627 E. Kings Canyon, Ste 156, Fresno, CA 93727, or call 1 (800) 873-0786.**

FAMILY PRACTICE PHYSICIAN. An exciting opportunity exists for the right Family Practice physician on the central coast of California. Join an active community medical center practice delivering care to inpatients and outpatients in rural area adjacent to communities of 50,000. Superb salary and benefit package. Spanish/English speaking preferred, but not required. BC preferred. Call or write Nipomo Community Medical Center, PO Box 430, Nipomo, CA 93444, attention Ronald E. Castle; (805) 929-3211.

EMERGENCY MEDICINE, New Mexico—Albuquerque. 14 physician group covering three hospitals. Must be BC/BE in Emergency Medicine. Competitive salary and benefits for region. Moderate volume and acuity. Excellent recreation and weather. Send CV to Medical Director, Emergency Department, 601 Grand NE, Albuquerque, NM 87102; or call (505) 848-8134.

MEDICAL DIRECTOR, BC/BE. Outpatient Family Practice—general Pediatrics, Internal Medicine, Gynecology, Prenatal care, Family Planning; lovely rural setting, mild climate in northern California's wine country, two hours north of San Francisco. Opportunity to treat variety of medical pathology, develop and implement programs to meet needs of Native American communities. Hospital privileges available if desired. Salary negotiable. Position open November 1, 1991. Contact Personnel, 564 South Dora St, #D, Ukiah, CA 95482; (707) 468-5341.

PHYSICIANS WANTED

CALIFORNIA MULTISPECIALTY. Dermatologist, Radiologist, Otorhinolaryngologist, General Surgeon, Cardiologist, Internal Medicine, Pediatrician, Gastroenterologist, Orthopedist, General/Family Practitioner, Obstetrician/Gynecologist. Excellent opportunity for physicians in Los Angeles suburb to join 100 member multispecialty medical group. Large fee-for-service and prepaid practice, no Medi-Cal. Excellent compensation program based on guarantee plus incentive, profit sharing and pension plan. Group provides health, dental, life, and malpractice. Partnership in real estate and medical corporation available. Send CV to Ron McDaniel, Assistant Administrator, Mullikin Medical Center—5, 17821 S. Pioneer Blvd, Artesia, CA 90701.

TACOMA. Independent or group practice opportunity available to Family Practitioner or Internal Medicine physician with emphasis on Geriatrics. Tacoma, ranked as 4th best city in the US, and nearby Gig Harbor are ideal communities for family, sailing, outdoor lifestyle. This affordable area is still being discovered and the rewards of medical practice are alive and well. For more information, please contact Ken Baker, President, Physician Search Group, 120 Montgomery St, Ste 710, San Francisco, CA 94104; (415) 399-8840.

PEDIATRICIANS—Southern California. Challenging career opportunities for Pediatricians desiring private practice. Growing, prestigious, university-affiliated south bay medical center is recruiting BC/BE physicians for expanding solo and group practices. Excellent compensation. Submit CV to J. Michaels, 2600 Cliff Dr, Newport Beach, CA 92663.

CALIFORNIA, MONTEREY BAY. Full-/part-time positions available with Monterey Bay's largest and most successful Urgent Care network. Generous guarantee, incentive plan, and benefit package. Malpractice covered. Practice in California's most beautiful coastal recreational area. BC/BE Emergency Room Medicine or Family Practice specialists preferred. Contact Bob Morris, MD, FACEP, Doctors on Duty Medical Clinics, 223 Mt Hermon Rd, Scotts Valley, CA 95066; (408) 438-9341.

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(Continued on Page 325)

(Continued from Page 324)

PHYSICIANS WANTED

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Good People. Good Medicine.

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Several positions available for Family Practice, Internal Medicine, and most medical subspecialties. We are a young, aggressive group in a well known prepaid group practice HMO organization with excellent benefits and a very reasonable call schedule. You will have a rewarding practice opportunity with ample time to enjoy the mountains and San Francisco which are nearby. If interested please call or send CV to Physician Recruitment, Administration, The Permanente Medical Group, Inc, 1305 Tommydon St, Stockton, CA 95210; (209) 476-3300.

FAMILY PRACTICE-HOSPITAL SPONSORED CLINIC OPPORTUNITY. Dynamic, growth oriented hospital in beautiful north central Wisconsin is seeking Family Physicians to join a growing practice in a new facility. The administrative burdens of medical practice will be minimized in this hospital managed clinic. The hospital has committed to an income and benefit package which is significantly higher than similar opportunities. Package includes base income, incentive bonus, malpractice, disability, signing bonus and student loan reduction/forgiveness program. All relocation costs will be borne by the hospital. Please contact Kari Wangsness, Associate, The Chancellor Group, Inc, France Place, Ste 920, 3601 Minnesota Dr, Bloomington, MN 55435; (612) 835-5123.

FAMILY PRACTITIONER (BC/BE) WANTED to join the staff of our suburban satellite clinic in Renton. The city of Renton is located at the south end of Lake Washington and is a short distance from many beaches, parks, and rivers that will accommodate fishing, boating, swimming, and picnicking. Numerous mountains are within easy commute that offer snow skiing as well as year round hiking. Renton and its surrounding communities have many fine residential neighborhoods and good schools. A diverse patient population includes managed care, fee-for-service, and retired military. Competitive salary and excellent benefits. Contact Mary Anderson, Pacific Medical Center, 1200 12th Ave S, Seattle, WA 98144; (206) 326-4100.

SAN JOSE. Primary Care group affiliated with a premier community hospital seeks Internal Medicine physician and Family Practitioner. The practice is located within an hour of beaches, mountains, and San Francisco. Only one block from the hospital. Salary plus benefits with partnership in two years. For more information, please contact Ken Baker, President, Physician Search Group, 120 Montgomery St, Ste 710, San Francisco, CA 94104; (415) 399-8840.

SALT LAKE CITY. Urgent Care Clinic—upper middle class area. Growing six-year-old facility, excellent staff, flexible schedules. BC preferred. Industrial Care Clinic—Five-year-old prestigious group, largest in state, progressive and aggressive. BC preferred, should be strong in Orthopedics. Work Net, PO Box 26692, Salt Lake City, UT 84199-26692.

FAMILY PRACTITIONERS—Southern California and Seattle, Washington suburb. Private practice opportunities available with established physician in Panorama City. Opportunity to take over an established part-time practice in small community southeast of Los Angeles. Group practice in Seattle suburb. For details, call Eloise Gusman, (800) 535-7698 or send CV to PO Box 101656, Fort Worth, TX 76185.

PRACTICES AVAILABLE

CARMEL-PEBBLE BEACH, CALIFORNIA. Prime Internal Medicine practice available. Large patient population to draw from. Associated with established Internist. Contact Walter L. Holz, Jr, MD, 26485 Carmel Rancho Blvd, Carmel, CA 93923; (408) 624-1864.

SEATTLE FAMILY PRACTICE. $220,00 gross in 183 workdays per year, 96% collections, 43% overhead. No Obstetrics, minimal Medicare, modern facilities, beautiful office park, state-of-art equipment, congenial six-member call group; (206) 391-6782 (home).

NORTHERN CALIFORNIA SAN JOAQUIN VALLEY. Urban Family Practice for sale. $650,000 gross. Will help with transition. Inquire at PO Box 40, French Camp, CA 95231.

SAN DIEGO COUNTY. Family, Internal, OB/GYN, and Pediatric practices available. Long established—doctors retiring. Various prices and low down payments. Call CBI, San Diego County's professional practice sales specialists, (619) 283-7009.

COLORADO COLLEGE TOWN. General Internal Medicine and Geriatric practice and building for sale. $125,000, variable terms. Solo corporation. Great place to live. Call (303) 226-8661 evenings.

UNIQUE SEMI-RETIREMENT PRACTICE for sale to Internist/Cardiologist interested in preventive medicine. State capital in southwest Washington. No third party billing for executive checkups and treadmill stress tests in no-overhead office in large athletic club. All equipment included. Easily gross 60K working part-time and take summers off. You move in. I move out. For 30K. Contact Stu Pritchard, MD; (206) 352-4884.

NORTHERN AND CENTRAL CALIFORNIA. Established practices available in Dermatology, Ophthalmology, Internal Medicine, Allergy/Preventive Medicine, and Family Practice. Reasonable terms and prices. Call/write Bradshaw Associates, 21 Altamount, Orinda, CA 94563; (415) 376-0762.

LAKE ARROWHEAD, CALIFORNIA. Well established, busy, profitable Family Practice in mountain resort community. Owner highly motivated. Relocating to east coast. Reply to Arthur S. Shorr & Associates, Inc, Consultants to Healthcare Providers at 21931 Burbank Blvd, #30, Woodland Hills, CA 91367; or call (818) 348-6632.

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(Continued on Page 326)

(Continued from Page 325)

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Anaheim, CA. Fees: $400 for ACC members; $450 for non-members; $250 for residents, fellows-in-training, nurses, and technicians. 18.5 category 1 credit hours. For information, call **American College of Cardiology; (800) 253-4636, ext 695; FAX: (301) 897-9745.**

TWENTY-THIRD ANNUAL CARDIOVASCULAR CONFERENCE AT SNOWMASS. January 13-17, 1992. Snowmass, Colorado. Fees: $450 for ACC members; $545 for non-members; $270 for residents, fellows-in-training, nurses, and technicians. 19.5 category 1 credit hours. For information, call **American College of Cardiology; (800) 253-4636, ext 695; FAX (301) 897-9745.**

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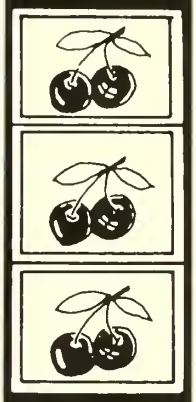

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Arizona Medical Association, Inc—810 W Bethany Home Rd, Phoenix 85013. (602) 246-8901. Annual Meeting: June 4-6, 1992, Scottsdale.

California Medical Association—PO Box 7690, San Francisco 94120-7690. (415) 541-0900. Annual Meeting: March 13-18, 1992, Disneyland Hotel, Anaheim.

Colorado Medical Society—PO Box 17550, Denver 80217-0550. (303) 779-5455. Annual Meeting: September 20-22, 1991, Snowmass.

Hawaii Medical Association—1360 S Beretania, Honolulu 96814. (808) 536-7702. Annual Meeting: October 11-13, 1991, Westin Kauai.

Idaho Medical Association—305 W Jefferson, PO Box 2668, Boise 83701. (208) 344-7888. Annual Meeting: 1992, date and location to be announced.

Montana Medical Association—2012 11th Ave, Suite 12, Helena 59601. (406) 443-4000. Annual Meeting: October 3-4, 1991, Kalispell.

Nevada State Medical Association—3660 Baker Lane, Reno 89502. (702) 825-6788. Annual Meeting: April 23-26, 1992, Sheraton Grand Torrey Pines, La Jolla, California.

New Mexico Medical Society—7770 Jefferson, Suite 400, Albuquerque 87109. (505) 828-0237. Annual Meeting: May 14-16, 1992, Albuquerque.

Oregon Medical Association—5210 SW Corbett Ave, Portland 97201. (503) 226-1555. Annual Meeting (House of Delegates only): 1992, date and location to be announced.

Utah Medical Association—540 E Fifth South, Salt Lake City 84102. (801) 355-7477. Annual Meeting: September 11-13, 1991, University Park Hotel, Salt Lake City.

Washington State Medical Association—900 United Airlines Bldg, 2033 6th Ave, Seattle 98121. (206) 441-WSMA. Annual Meeting: September 19-22, 1991, Red Lion, Bellevue.

Wyoming Medical Society—PO Drawer 4009, Cheyenne 82003-4009. (307) 635-2424. Annual Meeting: June 11-13, 1992, Jackson Lake Lodge, Moran.

ADVERTISING INDEX

BLUE CROSS OF CALIFORNIA 217

BLUE SHIELD OF CALIFORNIA 239

CIGNA HEALTHPLAN 319

CLASSIFIED ADVERTISING 316, 318, 319, 320, 322, 323, 324, 325, 326

COLUMBINE HOSPITAL
Eating Treatment Center 245

COSTAL GOVERNMENT SERVICES 323

COUNTY OF RIVERSIDE 323

DOCTORS' COMPANY 223

ELI LILLY & COMPANY
Axid 234, 235, 314, 315

GLAXO INC.
Zantac ..... 3rd and 4th covers

KAISER PERMANENTE 324

THE LANCET 243

MERCK SHARP & DOHME
Mevacor 229, 230, 231, 232

PALISADES PHARMACEUTICALS INC.
Yocon 215

PHYSICIAN LEADERSHIP INSTITUTE 235

PHYSICIANS INTERINDEMNITY INSURANCE 241

ROERIG
Cardura 225, 226

G.D. SEARLE & COMPANY
Calan SR 218, 313

UNIVERSITY MICROFILM 215

UNIVERSITY SOUTHERN CALIFORNIA
University Hospital 237

UPJOHN COMPANY
Ragaine ..... 2nd cover, 213, 247, 248

US AIR FORCE 317

US ARMY RESERVE 321

WELLS FARGO BANK 221

THE WESTERN JOURNAL OF MEDICINE
Special Issues 246
Subscription 213, 315

One Of A Kind

Zantac®

ranitidine HCl/Glaxo 150 mg and 300 mg tablets

Zantac® 150 Tablets
(ranitidine hydrochloride)

Zantac® 300 Tablets
(ranitidine hydrochloride)

Zantac® Syrup
(ranitidine hydrochloride)

BRIEF SUMMARY

The following is a brief summary only. Before prescribing, see complete prescribing information in Zantac® product labeling.

INDICATIONS AND USAGE: Zantac® is indicated in:
1. Short-term treatment of **active duodenal ulcer.** Most patients heal within four weeks.
2. **Maintenance therapy** for duodenal ulcer patients at reduced dosage after healing of acute ulcers.
3. The treatment of **pathological hypersecretory conditions** (eg, Zollinger-Ellison syndrome and systemic mastocytosis).
4. Short-term treatment of **active, benign gastric ulcer.** Most patients heal within six weeks and the usefulness of further treatment has not been demonstrated.
5. Treatment of **gastroesophageal reflux disease (GERD).** Symptomatic relief commonly occurs within one or two weeks after starting therapy. Therapy for longer than six weeks has not been studied.

In active duodenal ulcer; active, benign gastric ulcer; hypersecretory states; and GERD, concomitant antacids should be given as needed for relief of pain.

CONTRAINDICATIONS: Zantac® is contraindicated for patients known to have hypersensitivity to the drug.

PRECAUTIONS:

General: 1. Symptomatic response to Zantac® therapy does not preclude the presence of gastric malignancy.
2. Since Zantac is excreted primarily by the kidney, dosage should be adjusted in patients with impaired renal function (see DOSAGE AND ADMINISTRATION). Caution should be observed in patients with hepatic dysfunction since Zantac is metabolized in the liver.

Laboratory Tests: False-positive tests for urine protein with Multistix® may occur during Zantac therapy, and therefore testing with sulfosalicylic acid is recommended.

Drug Interactions: Although Zantac has been reported to bind weakly to cytochrome P-450 *in vitro*, recommended doses of the drug do not inhibit the action of the cytochrome P-450-linked oxygenase enzymes in the liver. However, there have been isolated reports of drug interactions that suggest that Zantac may affect the bioavailability of certain drugs by some mechanism as yet unidentified (eg, a pH-dependent effect on absorption or a change in volume of distribution).

Carcinogenesis, Mutagenesis, Impairment of Fertility: There was no indication of tumorigenic or carcinogenic effects in lifespan studies in mice and rats at doses up to 2,000 mg/kg/d.

Ranitidine was not mutagenic in standard bacterial tests (*Salmonella, Escherichia coli*) for mutagenicity at concentrations up to the maximum recommended for these assays.

In a dominant lethal assay, a single oral dose of 1,000 mg/kg to male rats was without effect on the outcome of two matings per week for the next nine weeks.

Pregnancy: ***Teratogenic Effects: Pregnancy Category B:*** Reproduction studies have been performed in rats and rabbits at doses up to 160 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to Zantac. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: Zantac is secreted in human milk. Caution should be exercised when Zantac is administered to a nursing mother.

Pediatric Use: Safety and effectiveness in children have not been established.

Use in Elderly Patients: Ulcer healing rates in elderly patients (65 to 82 years of age) were no different from those in younger age groups. The incidence rates for adverse events and laboratory abnormalities were also not different from those seen in other age groups.

ADVERSE REACTIONS: The following have been reported as events in clinical trials or in the routine management of patients treated with Zantac®. The relationship to Zantac therapy has been unclear in many cases. Headache, sometimes severe, seems to be related to Zantac administration.

Central Nervous System: Rarely, malaise, dizziness, somnolence, insomnia, and vertigo. Rare cases of reversible mental confusion, agitation, depression, and hallucinations have been reported, predominantly in severely ill elderly patients. Rare cases of reversible blurred vision suggestive of a change in accommodation have been reported.

Cardiovascular: As with other H_2-blockers, rare reports of arrhythmias such as tachycardia, bradycardia, atrioventricular block, and premature ventricular beats.

Gastrointestinal: Constipation, diarrhea, nausea/vomiting, abdominal discomfort/pain, and rare reports of pancreatitis.

Hepatic: In normal volunteers, SGPT values were increased to at least twice the pretreatment levels in 6 of 12 subjects receiving 100 mg qid intravenously for seven days, and in 4 of 24 subjects receiving 50 mg qid intravenously for five days. There have been occasional reports of hepatitis, hepatocellular or hepatocanalicular or mixed, with or without jaundice. In such circumstances, ranitidine should be immediately discontinued. These events are usually

Zantac® 150 and 300 (ranitidine hydrochloride) Tablets
Zantac® (ranitidine hydrochloride) Syrup

reversible, but in exceedingly rare circumstances death has occurred.

Musculoskeletal: Rare reports of arthralgias.

Hematologic: Blood count changes (leukopenia, granulocytopenia, thrombocytopenia) have occurred in a few patients. These were usually reversible. Rare cases of agranulocytosis, pancytopenia, sometimes with marrow hypoplasia, and aplastic anemia have been reported.

Endocrine: Controlled studies in animals and man have shown no stimulation of any pituitary hormone by Zantac and no antiandrogenic activity, and cimetidine-induced gynecomastia and impotence in hypersecretory patients have resolved when Zantac has been substituted. However, occasional cases of gynecomastia, impotence, and loss of libido have been reported in male patients receiving Zantac, but the incidence did not differ from that in the general population.

Integumentary: Rash, including rare cases suggestive of mild erythema multiforme, and, rarely, alopecia.

Other: Rare cases of hypersensitivity reactions (eg, bronchospasm, fever, rash, eosinophilia), anaphylaxis, angioneurotic edema, and small increases in serum creatinine.

OVERDOSAGE: Information concerning possible overdosage and its treatment appears in the full prescribing information.

DOSAGE AND ADMINISTRATION: (See complete prescribing information in Zantac® product labeling).

Active Duodenal Ulcer: The current recommended adult oral dosage is 150 mg or 10 ml (2 teaspoonfuls equivalent to 150 mg of ranitidine) twice daily. An alternate dosage of 300 mg or 20 ml (4 teaspoonfuls equivalent to 300 mg of ranitidine) once daily at bedtime can be used for patients in whom dosing convenience is important. The advantages of one treatment regimen compared to the other in a particular patient population have yet to be demonstrated.

Maintenance Therapy: The current recommended adult oral dosage is 150 mg or 10 ml (2 teaspoonfuls equivalent to 150 mg of ranitidine) at bedtime.

Pathological Hypersecretory Conditions (such as Zollinger-Ellison syndrome): The current recommended adult oral dosage is 150 mg or 10 ml (2 teaspoonfuls equivalent to 150 mg of ranitidine) twice a day. In some patients it may be necessary to administer Zantac® 150-mg doses more frequently. Doses should be adjusted to individual patient needs, and should continue as long as clinically indicated. Doses up to 6 g/d have been employed in patients with severe disease.

Benign Gastric Ulcer: The current recommended adult oral dosage is 150 mg or 10 ml (2 teaspoonfuls equivalent to 150 mg of ranitidine) twice a day.

GERD: The current recommended adult oral dosage is 150 mg or 10 ml (2 teaspoonfuls equivalent to 150 mg of ranitidine) twice a day.

Dosage Adjustment for Patients with Impaired Renal Function: On the basis of experience with a group of subjects with severely impaired renal function treated with Zantac, the recommended dosage in patients with a creatinine clearance less than 50 ml/min is 150 mg or 10 ml (2 teaspoonfuls equivalent to 150 mg of ranitidine) every 24 hours. Should the patient's condition require, the frequency of dosing may be increased to every 12 hours or even further with caution. Hemodialysis reduces the level of circulating ranitidine. Ideally, the dosage schedule should be adjusted so that the timing of a scheduled dose coincides with the end of hemodialysis.

HOW SUPPLIED: Zantac® 300 Tablets (ranitidine hydrochloride equivalent to 300 mg of ranitidine) are yellow, capsule-shaped tablets embossed with "ZANTAC 300" on one side and "Glaxo" on the other. They are available in bottles of 30 (NDC 0173-0393-40) tablets and unit dose packs of 100 (NDC 0173-0393-47) tablets.

Zantac® 150 Tablets (ranitidine hydrochloride equivalent to 150 mg of ranitidine) are white tablets embossed with "ZANTAC 150" on one side and "Glaxo" on the other. They are available in bottles of 60 (NDC 0173-0344-42) and 100 (NDC 0173-0344-09) tablets and unit dose packs of 100 (NDC 0173-0344-47) tablets.

Store between 15° and 30° C (59° and 86° F) in a dry place. Protect from light. Replace cap securely after each opening.

Zantac® Syrup, a clear, peppermint-flavored liquid, contains 16.8 mg of ranitidine hydrochloride equivalent to 15 mg of ranitidine per 1 ml in bottles of 16 fluid ounces (one pint) (NDC 0173-0383-54).

Store between 4° and 25° C (39° and 77° F). Dispense in tight, light-resistant containers as defined in the USP/NF.

July 1990

Glaxo Pharmaceuticals
DIVISION OF GLAXO INC.
Research Triangle Park, NC 27709

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Medi-Cal Approved

One Of A Kind

Please see Brief Summary of Prescribing Information on adjacent page.

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The Western Journal of Medicine

VOLUME 155 • NUMBER 4 OCTOBER 1991

BIOMEDICAL SCIENCE

365 Mechanisms and Consequences of Leukocyte-Endothelial Interaction
J M HARLAN, N B VEDDER, R K WINN, and C L RICE

ARTICLES

370 Helmet Use Improves Outcomes After Motorcycle Accidents
M A MURDOCK and K WAXMAN

373 Cardiac Dysfunction in Patients Seropositive for the Human Immunodeficiency Virus
J E JOHNSON, D M SLIFE, G T ANDERS, S R BAILEY, H M BLANTON, C K McALLISTER, and R D LATHAM

380 Patterns of Primary Care of Patients Infected With Human Immunodeficiency Virus
M D WENRICH and P G RAMSEY

384 Evaluating Cancer Patients for Rehabilitation Potential
D M O'TOOLE and A M GOLDEN

CONFERENCES AND REVIEWS

388 Molecular Genetics of Retinitis Pigmentosa
Moderator: D B FARBER
Discussants: J R HECKENLIVELY, R S SPARKES, and J B BATEMAN

400 *Vibrio vulnificus*—Hazard on the Half Shell
K L KOENIG, J MUELLER, and T ROSE

EPITOMES

404 Important Advances in General Surgery

ALERTS, NOTICES, AND CASE REPORTS

410 Fulminant Hepatic Failure Following Low-Dose Sustained-Release Niacin Therapy in Hospital
D J FISCHER, L L KNIGHT, and R E VESTAL

412 Gastric Tuberculosis Presenting as Fever of Unknown Origin
S R SALPETER, R M SHAPIRO, and J D GASMAN

413 Mouse Joint—Another Manifestation of an Occupational Epidemic?
L A NORMAN

415 Cisplatin Therapy-Associated Recurrent Toxic Shock Syndrome
A C BERMAN and L R BOLY

416 Hepatocellular Carcinoma Coexisting With Hepatic Adenoma—Incidental Discovery After Long-Term Oral Contraceptive Use
J KORULA, A YELLIN, G KANEL, G CAMPOFIORI, and P NICHOLS

RADIOLOGIC CASE

419 Acute Mediastinal Widening Following Endotracheal Intubation and Gastric Lavage
K PADMANABHAN, H GADDE, and S VORA

EDITORIALS

421 More Great News for Readers • Medical Student Section • A Lethal Leviathan—*Vibrio vulnificus* • Molecular Advances in Retinitis Pigmentosa • Niacin—The Long and the Short of It • Preceptorships in the 21st Century—The Return of the Apprentice

CORRESPONDENCE

428 Public Interest in Human Growth Hormone Therapy • Tort Reform Works • Medical Tourists • The Menace of Alcohol • Perspectives on 'Impairment' • The Value of Defiance

OTHER FEATURES

333 Subscription Information

342 Continuing Medical Education Activities in Arizona; California, Hawaii, and Nevada; Colorado; Idaho; New Mexico; Utah; Washington; Wyoming

361 Instructions for Authors

433 Classified Advertising

444 Western State Medical Associations' Meetings

Poems: 369, 432

Detailed Table of Contents: 334, 340, 344

Official Journal of the Alaska State Medical Association, the Arizona Medical Association, the California Medical Association, the Denver Medical Society, the Idaho Medical Association, the Nevada State Medical Association, the New Mexico Medical Society, the Utah Medical Association, the Washington State Medical Association, and the Wyoming Medical Society.

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Treat hypertension at its source with...

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CARDURA®

(doxazosin mesylate) Scored Tablets 1 mg, 2 mg, 4 mg, 8 mg

CARDURA is well tolerated. Only three common side effects were different from placebo: dizziness, somnolence, and fatigue. These were generally mild and transient; only 2% of patients in placebo-controlled studies discontinued due to adverse effects—the same rate as placebo. Syncope has been reported, but rarely (< 1%).

Please see brief summary of prescribing information on adjacent page of this advertisement.

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ONCE-A-DAY

CARDURA®

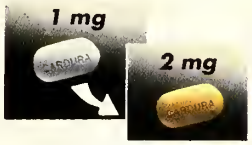
doxazosin mesylate | Scored Tablets 1 mg, 2 mg, 4 mg, 8 mg

Convenient once-a-day dosage

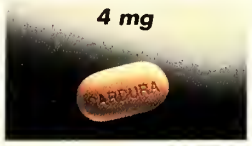
Most responsive patients are controlled with one daily dose of 4 to 8 mg[1]

—recommended initial dose is 1 mg, with dosage range of 1 mg to 16 mg per day.

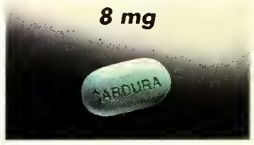
1 ***Begin all patients with CARDURA 1 mg once daily to minimize side effects. Evaluate supine and standing blood pressure. Prescribe CARDURA 2 mg once daily, if necessary.***



2 ***Evaluate for blood pressure control. Prescribe 4 mg once daily, if necessary.***



3 ***Evaluate for blood pressure control. Prescribe 8 mg once daily, if necessary. Maximum recommended dosage is 16 mg once daily.***



Reference: 1. Data available on request from Roerig

CAROURA® (doxazosin mesylate) Tablets
Brief Summary of Prescribing Information

INDICATIONS AND USAGE

CARDURA (doxazosin mesylate) is indicated for the treatment of hypertension. CARDURA may be used alone or in combination with diuretics or beta-adrenergic blocking agents. There is limited experience with CARDURA in combination with angiotensin converting enzyme inhibitors or calcium channel blockers.

CONTRAINDICATIONS

CARDURA is contraindicated in patients with a known sensitivity to quinazolines (e.g. prazosin, terazosin).

WARNINGS

Syncope and "First-dose" Effect:

Doxazosin, like other alpha-adrenergic blocking agents, can cause marked hypotension, especially in the upright position, with syncope and other postural symptoms such as dizziness. Marked orthostatic effects are most common with the first dose but can also occur when there is a dosage increase, or if therapy is interrupted for more than a few days. To decrease the likelihood of excessive hypotension and syncope, it is essential that treatment be initiated with the 1 mg dose. The 2, 4, and 8 mg tablets are not for initial therapy. Dosage should then be adjusted slowly (see DOSAGE AND ADMINISTRATION section) with increases in dose every two weeks. Additional antihypertensive agents should be added with caution.

Patients being titrated with doxazosin should be cautioned to avoid situations where injury could result should syncope occur.

In an early investigational study of the safety and tolerance of increasing daily doses of doxazosin in normotensives beginning at 1 mg/day, only 2 of 6 subjects could tolerate more than 2 mg/day without experiencing symptomatic postural hypotension. In another study of 24 healthy normotensive male subjects receiving initial doses of 2 mg/day of doxazosin, seven (29%) of the subjects experienced symptomatic postural hypotension between 0.5 and 6 hours after the first dose necessitating termination of the study. In this study 2 of the normotensive subjects experienced syncope. Subsequent trials in hypertensive patients always began doxazosin dosing at 1 mg/day resulting in a 4% incidence of postural side effects at 1 mg/day with no cases of syncope.

In multiple dose clinical trials involving over 1500 patients with dose titration every one to two weeks, syncope was reported in 0.7% of patients. None of these events occurred at the starting dose of 1 mg and 1.2% (8/664) occurred at 16 mg/day.

If syncope occurs, the patient should be placed in a recumbent position and treated supportively as necessary.

PRECAUTIONS

General:

1. Orthostatic Hypotension:

While syncope is the most severe orthostatic effect of CARDURA, other symptoms of lowered blood pressure, such as dizziness, lightheadedness, or vertigo, can occur, especially at initiation of therapy or at the time of dose increases. These were common in clinical trials, occurring in up to 23% of all patients treated and causing discontinuation of therapy in about 2%.

In placebo controlled titration trials orthostatic effects were minimized by beginning therapy at 1 mg per day and titrating every two weeks to 2, 4, or 8 mg per day. There was an increased frequency of orthostatic effects in patients given 8 mg or more, 10%, compared to 5% at 1-4 mg and 3% in the placebo group.

Patients in occupations in which orthostatic hypotension could be dangerous should be treated with particular caution.

If hypotension occurs, the patient should be placed in the supine position and, if this measure is inadequate, volume expansion with intravenous fluids or vasopressor therapy may be used. A transient hypotensive response is not a contraindication to further doses of CARDURA.

2. Impaired liver function:

CARDURA should be administered with caution to patients with evidence of impaired hepatic function or to patients receiving drugs known to influence hepatic metabolism (see CLINICAL PHARMACOLOGY). There is no controlled clinical experience with CARDURA in patients with these conditions.

3. Leukopenia/Neutropenia:

Analysis of hematologic data from patients receiving CARDURA in controlled clinical trials showed that the mean W8C (N=474) and mean neutrophil counts (N=419) were decreased by 2.4% and 1.0% respectively, compared to placebo, a phenomenon seen with other alpha blocking drugs. A search through a data base of 2400 patients revealed 4 in which drug-related neutropenia could not be ruled out. Two had a single low value on the last day of treatment. Two had stable, non-progressive neutrophil counts in the 1000/mm^3 range over periods of 20 and 40 weeks. In cases where follow-up was available the W8Cs and neutrophil counts returned to normal after discontinuation of CARDURA. No patients became symptomatic as a result of the low W8C or neutrophil counts.

Information for Patients:

Patients should be made aware of the possibility of syncopal and orthostatic symptoms, especially at the initiation of therapy, and urged to avoid driving or hazardous tasks for 24 hours after the first dose, after a dosage increase, and after interruption of therapy when treatment is resumed. They should be cautioned to avoid situations where injury could result should syncope occur during initiation of doxazosin therapy. They should also be advised of the need to sit or lie down when symptoms of lowered blood pressure occur, although these symptoms are not always orthostatic, and to be careful when rising from a sitting or lying position. If dizziness, lightheadedness, or palpitations are bothersome they should be reported to the physician, so that dose adjustment can be considered. Patients should also be told that drowsiness or somnolence can occur with doxazosin, requiring caution in people who must drive or operate heavy machinery.

Drug Interactions:

Most (98%) of plasma doxazosin is protein bound. *In vitro* data in human plasma indicate that CARDURA has no effect on protein binding of digoxin, warfarin, phenytoin or indomethacin. There is no information on the effect of other highly plasma protein bound drugs on doxazosin binding. CARDURA has been administered without any evidence of an adverse drug interaction to patients receiving thiazide diuretics, beta blocking agents, and nonsteroidal anti-inflammatory drugs.

Drug/Laboratory test interactions:

None known.

Cardiac Toxicity in Animals:

An increased incidence of myocardial necrosis or fibrosis was displayed by Sprague-Dawley rats after 6 months of dietary administration at concentrations calculated to provide 80 mg doxazosin/kg/day and after 12 months of dietary administration at concentrations calculated to provide 40 mg doxazosin/kg/day (150 times the maximum recommended human dose assuming a patient weight of 60 kg). There is no evidence that similar lesions occur in humans.

Carcinogenesis, Mutagenesis and Impairment of Fertility:

Chronic dietary administration (up to 24 months) of doxazosin mesylate at maximally tolerated concentrations (highest dose 40 mg/kg, about 150 times the maximum recommended human dose of 16 mg/60 kg) revealed no evidence of carcinogenicity in rats. There was also no evidence of carcinogenicity in a similarly conducted study (up to 18 months of dietary administration) in mice. The mouse study, however, was compromised by the failure to use a maximally tolerated dose of doxazosin.

Mutagenicity studies revealed no drug- or metabolite-related effects at either chromosomal or subchromosomal levels.

Studies in rats showed reduced fertility in males treated with doxazosin at oral doses of 20 (but not 5 or 10) mg/kg/day, about 75 times the maximum recommended human dose. This effect was reversible within two weeks of drug withdrawal.

Pregnancy

Teratogenic Effects, Pregnancy Category B. Studies in rabbits and rats at daily oral doses of up to 40 and 20 mg/kg, respectively (150 and 75 times the maximum recommended daily dose of 16 mg, assuming a patient weight of 60 kg), have revealed no evidence of harm to the fetus. The rabbit study, however, was compromised by the failure to use a maximally tolerated dose of doxazosin. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, CARDURA should be used during pregnancy only if clearly needed.

Radioactivity was found to cross the placenta following oral administration of labelled doxazosin to pregnant rats.

Nonteratogenic Effects. In peri-postnatal studies in rats, postnatal development at maternal doses of 40 or 50 mg/kg/day of doxazosin was delayed as evidenced by slower body weight gain and a slightly later appearance of anatomical features and reflexes.

Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when CARDURA is administered to a nursing mother.

Pediatric Use

Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

CARDURA has been administered to approximately 4000 patients, of whom 1679 were included in the clinical development program. In that program, minor adverse effects were frequent, but led to discontinuation of treatment in only 7% of patients. In placebo-controlled studies adverse effects occurred in 49% and 40% of patients in the doxazosin and placebo groups, respectively, and led to discontinuation in 2% of patients in each group. The major reasons for discontinuation were postural effects (2%), edema, malaise/fatigue, and some heart rate disturbance, each about 0.7%.

In controlled clinical trials directly comparing CARDURA to placebo there was no significant difference in the incidence of side effects, except for dizziness (including postural), weight gain, somnolence and fatigue/malaise. Postural effects and edema appeared to be dose related.

The prevalence rates presented below are based on combined data from placebo-controlled studies involving once daily administration of doxazosin at doses ranging from 1-16 mg. Table 1 summarizes those adverse experiences (possibly/probably related) reported for patients in these studies where the prevalence rate in the doxazosin group was at least 0.5% or where the reaction is of particular interest.

TABLE 1: ADVERSE REACTIONS DURING PLACEBO CONTROLLED STUDIES

		DOXAZOSIN (N=339)	PLACEBO (N=336)
CARDIOVASCULAR	Dizziness	19%	9%
	Vertigo	2%	1%
	Postural Hypotension	0.3%	0%
	Edema	4%	3%
	Palpitation	2%	3%
	Arrhythmia	1%	0%
	Hypotension	1%	0%
	Tachycardia	0.3%	1%
	Peripheral Ischemia	0.3%	0%
SKIN APPENDAGES	Rash	1%	1%
	Pruritus	1%	1%
MUSCULOSKELETAL	Arthralgia/Arthritis	1%	0%
	Muscle Weakness	1%	0%
	Myalgia	1%	0%
CENTRAL & PERIPHERAL N.S.	Headache	14%	16%
	Paresthesia	1%	1%
	Kinetic Disorders	1%	0%
	Ataxia	1%	0%
	Hypertonia	1%	0%
	Muscle Cramps	1%	0%
AUTONOMIC	Mouth Dry	2%	2%
	Flushing	1%	0%
SPECIAL SENSES	Vision Abnormal	2%	1%
	Conjunctivitis/Eye Pain	1%	1%
	Tinnitus	1%	0.3%
PSYCHIATRIC	Somnolence	5%	1%
	Nervousness	2%	2%
	Depression	1%	1%
	Insomnia	1%	1%
	Sexual Dysfunction	2%	1%
GASTROINTESTINAL	Nausea	3%	4%
	Diarrhea	2%	3%
	Constipation	1%	1%
	Dyspepsia	1%	1%
	Flatulence	1%	1%
	Abdominal Pain	0%	2%
	Vomiting	0%	1%
RESPIRATORY	Rhinitis	3%	1%
	Dyspnea	1%	1%
	Epistaxis	1%	0%
URINARY	Polyuria	2%	0%
	Urinary Incontinence	1%	0%
	Micturation Frequency	0%	2%
GENERAL	Fatigue/Malaise	12%	6%
	Chest Pain	2%	2%
	Asthenia	1%	1%
	Face Edema	1%	0%
	Pain	2%	2%

Additional adverse reactions have been reported, but these are, in general, not distinguishable from symptoms that might have occurred in the absence of exposure to doxazosin. The following adverse reactions occurred with a frequency of between 0.5% and 1%: syncope, hypoesthesia, increased sweating, agitation, increased weight. The following additional adverse reactions were reported by <0.5% of 3960 patients who received doxazosin in controlled or open, short- or long-term clinical studies, including international studies: *Cardiovascular System:* angina pectoris, myocardial infarction, cerebrovascular accident; *Autonomic Nervous System:* pallor; *Metabolic:* thirst, gout, hypokalemia; *Hematopoietic:* lymphadenopathy, purpura; *Reproductive System:* breast pain; *Skin Disorders:* alopecia, dry skin, eczema; *Central Nervous System:* paresis, tremor, twitching, confusion, migraine, impaired concentration; *Psychiatric:* paronirra, amnesia, emotional lability, abnormal thinking, depersonalization; *Special Senses:* parosmia, earache, taste perversion, photophobia, abnormal lacrimation; *Gastrointestinal System:* increased appetite, anorexia, fecal incontinence, gastroenteritis; *Respiratory System:* bronchospasm, sinusitis, coughing, pharyngitis; *Urinary System:* renal calculus; *General Body System:* hot flashes, back pain, infection, fever/rigors, decreased weight, influenza-like symptoms.

CARDURA has not been associated with any clinically significant changes in routine biochemical tests. No clinically relevant adverse effects were noted on serum potassium, serum glucose, uric acid, blood urea nitrogen, creatinine or liver function tests. CARDURA has been associated with decreases in white blood cell counts (See Precautions).

OVERDOSAGE

The oral LD_{50} of doxazosin is greater than 1000 mg/kg in mice and rats. The most likely manifestation of overdosage would be hypotension, for which the usual treatment would be intravenous infusion of fluid. As doxazosin is highly protein bound, dialysis would not be indicated.

DOSAGE AND ADMINISTRATION

DOSAGE MUST BE INDIVIDUALIZED. The initial dosage of CARDURA in hypertensive patients is 1 mg given once daily. Depending on the individual patient's standing blood pressure response (based on measurements taken at 2-6 hours postdose and 24 hours postdose), dosage may then be increased to 2 mg and thereafter if necessary to 4 mg, 8 mg and 16 mg to achieve the desired reduction in blood pressure. Increases in dose beyond 4 mg increase the likelihood of excessive postural effects including syncope, postural dizziness/vertigo, postural hypotension. At a titrated dose of 16 mg once daily the frequency of postural effects is about 12% compared to 3% for placebo.

HOW SUPPLIED

CARDURA (doxazosin mesylate) is available as colored tablets for oral administration. Each tablet contains doxazosin mesylate equivalent to 1 mg (white), 2 mg (yellow), 4 mg (orange) or 8 mg (green) of the active constituent, doxazosin.

CARDURA® TABLETS are available as 1 mg (white), 2 mg (yellow), 4 mg (orange) and 8 mg (green) scored tablets. Bottles of 100. 1 mg (NDC 0049-2750-66), 2 mg (NDC 0049-2760-66), 4 mg (NDC 0049-2770-66), 8 mg (NDC 0049-2780-66).

Recommended Storage: Store below 86°F(30°C).

CAUTION: Federal law prohibits dispensing without prescription.

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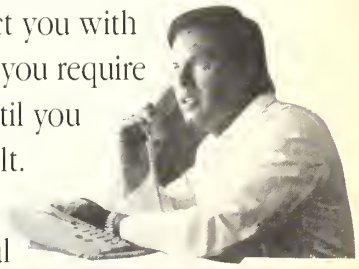

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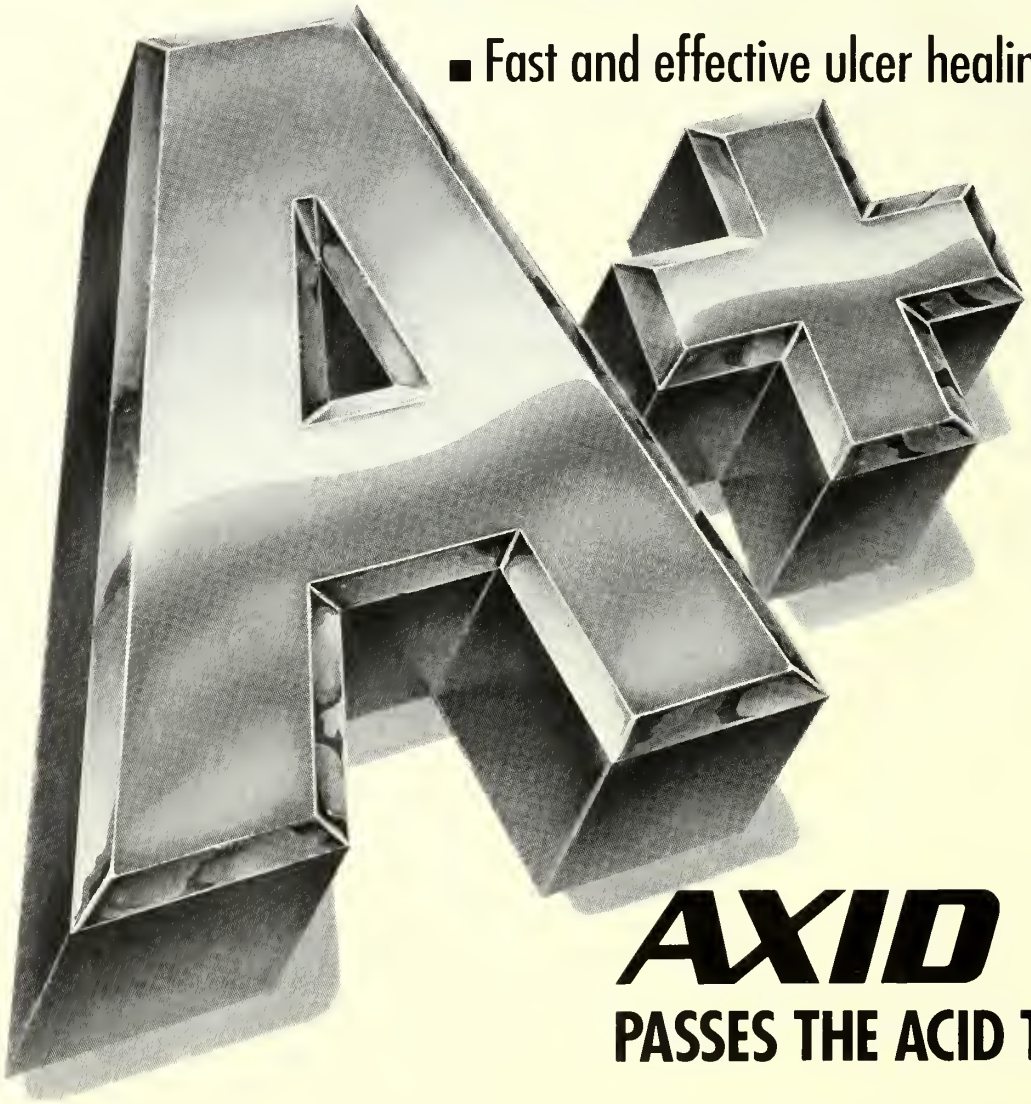

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See adjacent page for references and brief summary of prescribing information.

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AXID® (nizatidine capsules)

Brief Summary. Consult the package insert for complete prescribing information.
Indications and Usage: 1. *Active duodenal ulcer*—for up to 8 weeks of treatment. Most patients heal within 4 weeks.

2. *Maintenance therapy*—for healed duodenal ulcer patients at a reduced dosage of 150 mg h.s. The consequences of therapy with Axid for longer than 1 year are not known.

Contraindications: Known hypersensitivity to the drug. Because cross sensitivity in this class of compounds has been observed, H_2-receptor antagonists, including Axid, should not be administered to patients with a history of hypersensitivity to other H_2-receptor antagonists.

Precautions: *General*—1. Symptomatic response to nizatidine therapy does not preclude the presence of gastric malignancy.

2. Dosage should be reduced in patients with moderate to severe renal insufficiency.

3. In patients with normal renal function and uncomplicated hepatic dysfunction, the disposition of nizatidine is similar to that in normal subjects.

Laboratory Tests—False-positive tests for urobilinogen with Multistix® may occur during therapy.

Drug Interactions—No interactions have been observed with theophylline, chlordiazepoxide, lorazepam, lidocaine, phenytoin, and warfarin. Axid does not inhibit the cytochrome P-450 enzyme system, therefore, drug interactions mediated by inhibition of hepatic metabolism are not expected to occur. In patients given very high doses (3,900 mg) of aspirin daily, increased serum salicylate levels were seen when nizatidine, 150 mg b.i.d., was administered concurrently.

Carcinogenesis, Mutagenesis, Impairment of Fertility—A 2-year oral carcinogenicity study in rats with doses as high as 500 mg/kg/day (about 80 times the recommended daily therapeutic dose) showed no evidence of a carcinogenic effect. There was a dose-related increase in the density of enterochromaffin-like (ECL) cells in the gastric oxyntic mucosa. In a 2-year study in mice, there was no evidence of a carcinogenic effect in male mice, although hyperplastic nodules of the liver were increased in the high-dose males as compared with placebo. Female mice given the high dose of Axid (2,000 mg/kg/day, about 330 times the human dose) showed marginally statistically significant increases in hepatic carcinoma and hepatic nodular hyperplasia with no numerical increase seen in any of the other dose groups. The rate of hepatic carcinoma in the high-dose animals was within the historical control limits seen for the strain of mice used. The female mice were given a dose larger than the maximum tolerated dose, as indicated by excessive (30%) weight decrement as compared with concurrent controls and evidence of mild liver injury (transaminase elevations). The occurrence of a marginal finding at high dose only in animals given an excessive and somewhat hepatotoxic dose, with no evidence of a carcinogenic effect in rats, male mice, and female mice (given up to 360 mg/kg/day, about 60 times the human dose), and a negative mutagenicity battery are not considered evidence of a carcinogenic potential for Axid.

Axid was not mutagenic in a battery of tests performed to evaluate its potential genetic toxicity, including bacterial mutation tests, unscheduled DNA synthesis, sister chromatid exchange, mouse lymphoma assay, chromosome aberration tests, and a micronucleus test.

In a 2-generation, perinatal and postnatal fertility study in rats, doses of nizatidine up to 650 mg/kg/day produced no adverse effects on the reproductive performance of parental animals or their progeny.

Pregnancy—Teratogenic Effects—Pregnancy Category C—Oral reproduction studies in rats at doses up to 300 times the human dose and in Dutch Belted rabbits at doses up to 55 times the human dose revealed no evidence of impaired fertility or teratogenic effect; but, at a dose equivalent to 300 times the human dose, treated rabbits had abortions, decreased number of live fetuses, and depressed fetal weights. On intravenous administration to pregnant New Zealand White rabbits, nizatidine at 20 mg/kg produced cardiac enlargement, coarctation of the aortic arch, and cutaneous edema in 1 fetus, and at 50 mg/kg, it produced ventricular anomaly, distended abdomen, spina bifida, hydrocephaly, and enlarged heart in 1 fetus. There are, however, no adequate and well-controlled studies in pregnant women. It is also not known whether nizatidine can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Nizatidine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers—Studies in lactating women have shown that 0.1% of an oral dose is secreted in human milk in proportion to plasma concentrations. Because of growth depression in pups reared by treated lactating rats, a decision should be made whether to discontinue nursing or the drug, taking into account the importance of the drug to the mother.

Pediatric Use—Safety and effectiveness in children have not been established.

Use in Elderly Patients—Healing rates in elderly patients were similar to those in younger age groups as were the rates of adverse events and laboratory test abnormalities. Age alone may not be an important factor in the disposition of nizatidine. Elderly patients may have reduced renal function.

Adverse Reactions: Clinical trials of varying durations included almost 5,000 patients. Among the more common adverse events in domestic placebo-controlled trials of over 1,900 nizatidine patients and over 1,300 on placebo, sweating (1% vs 0.2%), urticaria (0.5% vs <0.01%), and somnolence (2.4% vs 1.3%) were significantly more common with nizatidine. It was not possible to determine whether a variety of less common events were due to the drug.

Hepatic—Hepatocellular injury (elevated liver enzyme tests or alkaline phosphatase) possibly or probably related to nizatidine occurred in some patients. In some cases, there was marked elevation (>500 IU/L) in SGOT or SGPT and, in a single instance, SGPT was >2,000 IU/L. The incidence of elevated liver enzymes overall and elevations of up to 3 times the upper limit of normal, however, did not significantly differ from that in placebo patients. All abnormalities were reversible after discontinuation of Axid. Since market introduction, hepatitis and jaundice have been reported. Rare cases of cholestatic or mixed hepatocellular and cholestatic injury with jaundice have been reported with reversal of the abnormalities after discontinuation of Axid.

Cardiovascular—In clinical pharmacology studies, short episodes of asymptomatic ventricular tachycardia occurred in 2 individuals administered Axid and in 3 untreated subjects.

CNS—Rare cases of reversible mental confusion have been reported.

Endocrine—Clinical pharmacology studies and controlled clinical trials showed no evidence of antiandrogenic activity due to nizatidine. Impotence and decreased libido were reported with equal frequency by patients on nizatidine and those on placebo. Gynecomastia has been reported rarely.

Hematologic—Fatal thrombocytopenia was reported in a patient treated with nizatidine and another H_2-receptor antagonist. This patient had previously experienced thrombocytopenia while taking other drugs. Rare cases of thrombocytopenic purpura have been reported.

Integumental—Sweating and urticaria were reported significantly more frequently in nizatidine- than in placebo-treated patients. Rash and exfoliative dermatitis were also reported.

Hypersensitivity—As with other H_2-receptor antagonists, rare cases of anaphylaxis following nizatidine administration have been reported. Rare episodes of hypersensitivity reactions (eg, bronchospasm, laryngeal edema, rash, and eosinophilia) have been reported.

Other—Hyperuricemia unassociated with gout or nephrolithiasis was reported. Eosinophilia, fever, and nausea related to nizatidine have been reported.

Overdosage: Overdoses of Axid have been reported rarely. If overdosage occurs, activated charcoal, emesis, or lavage should be considered along with clinical monitoring and supportive therapy. Renal dialysis does not substantially increase clearance of nizatidine due to its large volume of distribution.

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2. *Scand J Gastroenterol* 1987;22(suppl 136):61-70.
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4. *Am J Gastroenterol* 1989;84:769-774.

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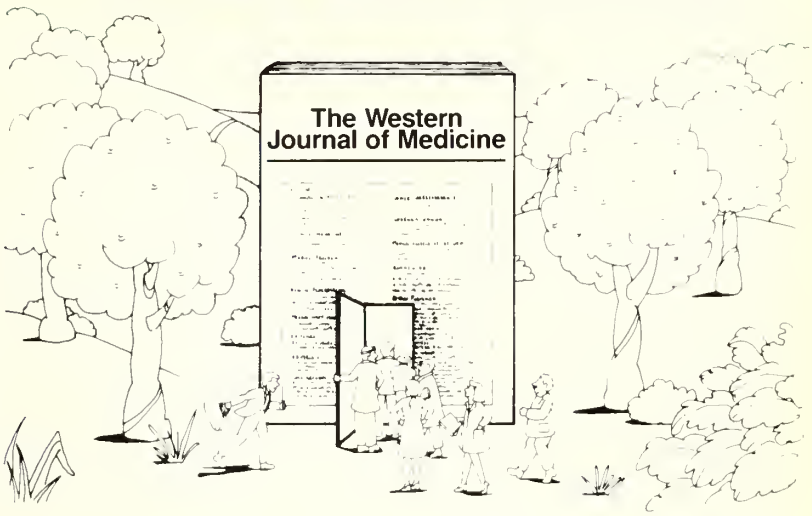

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VOLUME 155 • NUMBER 4 • OCTOBER 1991

CONTENTS

BIOMEDICAL SCIENCE

365 **Mechanisms and Consequences of Leukocyte-Endothelial Interaction**

JOHN M. HARLAN, MD; NICHOLAS B. VEDDER, MD; ROBERT K. WINN, PhD; and CHARLES L. RICE, MD

From the Department of Medicine, Division of Hematology, and the Department of Surgery, University of Washington School of Medicine, Seattle.

ARTICLES

370 **Helmet Use Improves Outcomes After Motorcycle Accidents**

MARGIE A. MURDOCK, RN, MSN, and KENNETH WAXMAN, MD

From the Department of Surgery, University of California Irvine Medical Center, Orange.

373 **Cardiac Dysfunction in Patients Seropositive for the Human Immunodeficiency Virus**

MAJ JAMES E. JOHNSON, MC, USA; MAJ DAVID M. SLIFE, MC, USA; MAJ GREGG T. ANDERS, MC, USA; STEVEN R. BAILEY, MD; MAJ HERMAN M. BLANTON, MC, USA; COL C. KENNETH McALLISTER, MC, USA; and MAJ RICKY D. LATHAM, MC, USA

From the Pulmonary Disease/Critical Care Service, Cardiology Service, and Infectious Disease Service, Brooke Army Medical Center, Fort Sam Houston, Texas.

380 **Patterns of Primary Care of Patients Infected With Human Immunodeficiency Virus**

MARJORIE D. WENRICH and PAUL G. RAMSEY, MD

From the Department of Medicine, University of Washington School of Medicine, Seattle.

384 **Evaluating Cancer Patients for Rehabilitation Potential**

DAVID M. O'TOOLE, MD, and ALICE M. GOLDEN, RN, MSN, MBA

From the Departments of Rehabilitation Medicine and Quality Assurance Services, Fairlawn Rehabilitation Hospital, Worcester, Massachusetts.

CONFERENCES AND REVIEWS

388 **Molecular Genetics of Retinitis Pigmentosa**

Moderator: DEBORA B. FARBER, PhD

Discussants: JOHN R. HECKENLIVELY, MD; ROBERT S. SPARKES, MD; and J. BRONWYN BATEMAN, MD

An edited summary of an Interdepartmental Conference arranged by the Department of Medicine of the UCLA School of Medicine, Los Angeles. The Director of Conferences is Anthony T. Compagnoni, PhD, Professor of Biobehavioral Sciences.

400 ***Vibrio vulnificus*—Hazard on the Half Shell**

KRISTI L. KOENIG, MD; JUERGEN MUELLER, MD; and THEODORE ROSE, MD

From the Division of Emergency Medicine, University of California Irvine Medical Center, Orange, and the Department of Medicine, Highland General Hospital, Oakland, California.

EPITOMES—IMPORTANT ADVANCES IN CLINICAL MEDICINE

General Surgery

Items of progress in general surgery. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance.

404 **Advances in the Management of Hemorrhagic Shock**

SCOTT R. MILLER, MD, and KENNETH WAXMAN, MD

405 **Use and Abuse of Parenteral Nutrition**

HOWARD SILBERMAN, MD

(Continued on Page 340)

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Contraindications: Hypersensitivity to buspirone hydrochloride
Warnings: The administration of BuSpar to a patient taking a monoamine oxidase inhibitor (MAOI) may pose a hazard. Since blood pressure has become elevated when BuSpar was administered concomitantly with an MAOI, such concomitant use is not recommended BuSpar should not be employed in lieu of appropriate antipsychotic treatment
Precautions: *General*—*Interference with cognitive and motor performance* Although buspirone is less sedating than other anxiolytics and does not produce significant functional impairment, its CNS effects in a given patient may not be predictable, therefore, patients should be cautioned about operating an automobile or using complex machinery until they are reasonably certain that buspirone does not affect them adversely Although buspirone has not been shown to increase alcohol-induced impairment in motor and mental performance, it is prudent to avoid concomitant use with alcohol
Potential for withdrawal reactions in sedative/hypnotic/anxiolytic drug dependent patients Because buspirone will not block the withdrawal syndrome often seen with cessation of therapy with benzodiazepines and other common sedative/hypnotic drugs, before starting buspirone withdraw patients gradually from their prior treatment, especially those who used a CNS depressant chronically Rebound or withdrawal symptoms may occur over varying time periods, depending in part on the type of drug and its elimination half-life The withdrawal syndrome can appear as any combination of irritability, anxiety, agitation, insomnia, tremor, abdominal cramps, muscle cramps, vomiting, sweating, flu-like symptoms without fever, and occasionally, even as seizures
Possible concerns related to buspirone's binding to dopamine receptors Because buspirone can bind to central dopamine receptors, a question has been raised about its potential to cause acute and chronic changes in dopamine mediated neurological function (eg, dystonia, pseudoparkinsonism, akathisia, and tardive dyskinesia) Clinical experience in controlled trials has failed to identify any significant neuroleptic-like activity, however, a syndrome of restlessness, appearing shortly after initiation of treatment, has been reported, the syndrome may be due to increased central noradrenergic activity or may be attributable to dopaminergic effects (ie, represent akathisia)
Information for Patients—Patients should be instructed to inform their physician about any medications, prescription or nonprescription, alcohol or drugs they are now taking or plan to take during treatment with buspirone, to inform their physician if they are pregnant, are planning to become pregnant, or become pregnant while taking buspirone, to inform their physician if they are breast feeding, and not to drive a car or operate potentially dangerous machinery until they experience how this medication affects them
Drug Interactions—Concomitant use with other CNS active drugs should be approached with caution (see **Warnings**) Concomitant use with trazodone may have caused 3- to 6-fold elevations on SGPT (ALT) in a few patients Concomitant administration of BuSpar and haloperidol resulted in increased serum haloperidol concentrations in normal volunteers The clinical significance is not clear Buspirone does not displace tightly bound drugs like phenytoin, propranolol, and wartarin from serum proteins, but may displace less firmly bound drugs like digoxin However, there was one report of prolonged prothrombin time when buspirone was given to a patient also treated with wartarin, phenytoin, phenobarbital, digoxin, and Synthroid
Carcinogenesis, Mutagenesis, Impairment of Fertility—*No* evidence of carcinogenic potential was observed in rats or mice, buspirone did not induce point mutations, nor was DNA damage observed, chromosomal aberrations or abnormalities did not occur
Pregnancy: Teratogenic Effects—Pregnancy Category B Should be used during pregnancy only if clearly needed
Nursing Mothers—Administration to nursing women should be avoided if clinically possible
Pediatric Use—The safety and effectiveness have not been determined in individuals below 18 years of age
Use in the Elderly—No unusual, adverse, age-related phenomena have been identified in elderly patients receiving a total modal daily dose of 15 mg
Use in Patients with Impaired Hepatic or Renal Function—Since buspirone is metabolized by the liver and excreted by the kidneys, it is not recommended in severe hepatic or renal impairment
Adverse Reactions (See also Precautions): *Commonly Observed*—The more commonly observed untoward events, not seen at an equivalent incidence in placebo-treated patients, include dizziness, nausea, headache, nervousness, lightheadedness, and excitement
Associated with Discontinuation of Treatment—The more common events causing discontinuation included central nervous system disturbances (3 4%), primarily dizziness, insomnia, nervousness, drowsiness, lightheaded feeling, gastrointestinal disturbances (1 2%), primarily nausea, miscellaneous disturbances (1 1%), primarily headache and fatigue In addition, 3 4% of patients had multiple complaints, none of which could be characterized as primary
Incidence in Controlled Clinical Trials—Adverse events reported by 1% or more of 477 patients who received buspirone in four-week, controlled trials *Cardiovascular* Tachycardia/palpitations 1% *CNS* Dizziness 12%, drowsiness 10%, nervousness 5%, insomnia 3%, lightheadedness 3%, decreased concentration 2%, excitement 2%, anger/hostility 2%, contusion 2%, depression 2% *EENT* Blurred vision 2% *Gastrointestinal* Nausea 8%, dry mouth 3%, abdominal/gastric distress 2%, diarrhea 2%, constipation 1%, vomiting 1% *Musculoskeletal* Musculoskeletal aches/pains 1% *Neurological* Numbness 2%, paresthesia 1%, incoordination 1%, tremor 1% *Skin* Skin rash 1% *Miscellaneous* Headache 6%, fatigue 4%, weakness 2%, sweating/clamminess 1%
Other Events Observed During the Entire Premarketing Evaluation—The relative frequency of all other undesirable events reasonably associated with the use of buspirone in approximately 3000 subjects who took multiple doses of the drug under well-controlled, open, and uncontrolled conditions is defined as follows Frequent are those occurring in at least 1/100 patients, infrequent are those occurring in 1/100 to 1/1000 patients, and rare are those occurring in less than 1/1000 patients *Cardiovascular*—frequent nonspecific chest pain, infrequent syncope, hypotension, hypertension, rare cerebrovascular accident, congestive heart failure, myocardial infarction, cardiomyopathy, bradycardia *Central Nervous System*—frequent dream disturbances, infrequent depersonalization, dysphoria, noise intolerance, euphoria, akathisia, tearfulness, loss of interest, dissociative reaction, hallucinations, suicidal ideation, seizures, rare feelings of claustrophobia, cold intolerance, stupor, slurred speech, psychosis *EENT*—frequent tinnitus, sore throat, nasal congestion, infrequent redness and itching of the eyes, altered taste, altered smell, conjunctivitis, rare inner ear abnormality, eye pain, photophobia, pressure on eyes *Endocrine*—rare galactorrhea, thyroid abnormality *Gastrointestinal*—infrequent flatulence, anorexia increased appetite, salivation, irritable colon, rectal bleeding, rare burning of the tongue *Genitourinary*—infrequent urinary frequency, urinary hesitancy, menstrual irregularity and spotting, dysuria, rare amenorrhea, pelvic inflammatory disease, enuresis, nocturia *Musculoskeletal*—infrequent muscle cramps, muscle spasms, rigid/stiff muscles, arthralgias *Neurological*—infrequent involuntary movements, slowed reaction time, rare muscle weakness *Respiratory*—infrequent hyperventilation, shortness of breath, chest congestion, rare epistaxis *Sexual Function*—infrequent decreased or increased libido, rare delayed ejaculation, impotence *Skin*—infrequent edema, pruritus, flushing, easy bruising, hair loss, dry skin, facial edema, blisters, rare acne, thinning of nails *Clinical Laboratory*—infrequent increases in hepatic aminotransferases (SGOT, SGPT), rare eosinophilia, leukopenia, thrombocytopenia *Miscellaneous*—infrequent weight gain, fever, roaring sensation in the head, weight loss, malaise, rare alcohol abuse, bleeding disturbance, loss of voice, hiccoughs
Postintroduction Clinical Experience—Rare occurrences of allergic reactions, cogwheel rigidity, dystonic reactions, ecchymosis, emotional lability, tunnel vision, and urinary retention have been reported Because of the uncontrolled nature of these spontaneous reports, a causal relationship to BuSpar has not been determined
Drug Abuse and Dependence: *Controlled Substance Class*—Not a controlled substance
Physical and Psychological Dependence—Buspirone has shown no potential for abuse or diversion and there is no evidence that it causes tolerance, or either physical or psychological dependence However, since it is difficult to predict from experiments the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of buspirone misuse or abuse (eg, development of tolerance, incrementation of dose, drug-seeking behavior)
Overdosage: *Signs and Symptoms*—At doses approaching 375 mg/day the following symptoms were observed nausea, vomiting, dizziness, drowsiness, miosis, and gastric distress No deaths have been reported in humans either with deliberate or accidental overdosage
Recommended Overdose Treatment—General symptomatic and supportive measures should be used along with immediate gastric lavage No specific antidote is known and dialyzability of buspirone has not been determined
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Vibrio vulnificus is an extremely invasive gram-negative bacillus that causes bacteremia and shock. It should be suspected in any patient who is immunocompromised or has liver disease or hemochromatosis. Reduced gastric acidity may also increase the risk of infection if a patient presents with a history of ingesting raw shellfish (especially oysters) or trauma in brackish waters and skin lesions. Patients most commonly present with one of three clinical syndromes: primary septicemia, wound infection, or gastroenteritis. Treatment includes aggressive wound debridement, antibiotic therapy, and supportive care. Rapidly diagnosing and promptly initiating therapy are critical because *V vulnificus* infection is rapidly progressive and mortality approaches 100% if septic shock occurs.

VIBRIO VULNIFICUS
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SEPTICEMIA
SEPTIC SHOCK
SHELLFISH INGESTION

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AIR FORCE

(Continued from Page 334)

405 **Procuring Donor Organs for Transplantation**
ROBERT C. MACKERSIE, MD

406 **Surgical Treatment of Chronic Ulcerative Colitis**
JAMES STONE, MD

407 **Efficacy of Carotid Endarterectomy in Randomized Trials**
WESLEY S. MOORE, MD

407 **Surgical Treatment of Hemoptysis**
JOHN R. BENFIELD, MD

408 **Laparoscopic Cholecystectomy**
BRUCE E. STABILE, MD

ALERTS, NOTICES, AND CASE REPORTS

410 **Fulminant Hepatic Failure Following Low-Dose Sustained-Release Niacin Therapy in Hospital**
DAVID J. FISCHER, MD; LAWRENCE L. KNIGHT, MD; and ROBERT E. VESTAL, MD

From the Medical and Laboratory Services and the Clinical Pharmacology and Gerontology Research Unit, Veterans Affairs Medical Center, Boise, Idaho, and the Departments of Medicine, Pharmacology, and Pathology, University of Washington School of Medicine, Seattle.

412 **Gastric Tuberculosis Presenting as Fever of Unknown Origin**
SHELLEY R. SALPETER, MD; RICHARD M. SHAPIRO, MD; and JOHN D. GASMAN, MD

From the Department of Medicine, Stanford University Medical Center, Stanford, California. Dr Salpeter is now with the Santa Clara Valley Medical Center, San Jose, California.

413 **Mouse Joint—Another Manifestation of an Occupational Epidemic?**
LEE A. NORMAN, MD, MHS

From the Family Practice Residency Program, Swedish Hospital Medical Center, and the Department of Family Medicine, University of Washington School of Medicine, Seattle.

415 **Cisplatin Therapy-Associated Recurrent Toxic Shock Syndrome**
ARNOLD C. BERMAN, MD, and LAWRENCE R. BOLY, MD

From the Department of Medicine, Mount Zion Hospital and Medical Center, San Francisco, California.

416 **Hepatocellular Carcinoma Coexisting With Hepatic Adenoma—Incidental Discovery After Long-Term Oral Contraceptive Use**
JACOB KORULA, MD; ALBERT YELLIN, MD; GARY KANEL, MD; GAIL CAMPOFIORI, MD; and PETER NICHOLS, MD

From the Departments of Medicine, Surgery, and Pathology, University of Southern California School of Medicine, and the USC Liver Unit, Rancho Los Amigos Medical Center, Los Angeles, California.

RADIOLOGIC CASE

419 **Acute Mediastinal Widening Following Endotracheal Intubation and Gastric Lavage**
KRISHNAN PADMANABHAN, MD; HARI GADDE, MD; and SAMIR VORA, MD

From the Pulmonary Department, Coney Island Hospital, Brooklyn, New York, and the Department of Medicine, State University of New York, Health Science Center at Brooklyn, College of Medicine.

EDITORIALS

421 **More Great News for Readers**

421 **Medical Student Section**
VALENTINA N. CHEN and ROBERT W. CUTLER, MD

Ms Chen is a third-year medical student and Dr Cutler is Senior Associate Dean for Faculty Affairs, Stanford University School of Medicine, Stanford, California.

(Continued on Page 344)

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ontraindications: Severe LV dysfunction (see *Warnings*), hypotension (systolic pressure 90 mm Hg) or cardiogenic shock, sick sinus syndrome (if no pacemaker is present), 2nd- or d-degree AV block (if no pacemaker is present), atrial flutter/fibrillation with an accessory pass tract (eg, WPW or LGL syndromes), hypersensitivity to verapamil.

arnings: Verapamil should be avoided in patients with severe LV dysfunction (eg, ejection action < 30%) or moderate to severe symptoms of cardiac failure and in patients with any gree of ventricular dysfunction if they are receiving a beta-blocker. Control milder heart failure ith optimum digitalization and/or diuretics before Calan SR is used. Verapamil may occasionally oduce hypotension. Elevations of liver enzymes have been reported. Several cases have been monstrated to be produced by verapamil. Periodic monitoring of liver function in patients on rapamil is prudent. Some patients with paroxysmal and/or chronic atrial flutter/fibrillation and accessory AV pathway (eg, WPW or LGL syndromes) have developed an increased antegrade nduction across the accessory pathway bypassing the AV node, producing a very rapid ntricular response or ventricular fibrillation after receiving I.V. verapamil (or digitalis). Because this risk, oral verapamil is contraindicated in such patients. AV block may occur (2nd- and d-degree, 0.8%). Development of marked 1st-degree block or progression to 2nd- or 3rd-gree block requires reduction in dosage or, rarely, discontinuation and institution of appropriate erapy. Sinus bradycardia, 2nd-degree AV block, sinus arrest, pulmonary edema and/or severe potension were seen in some critically ill patients with hypertrophic cardiomyopathy who were ated with verapamil.

ecautions: Verapamil should be given cautiously to patients with impaired hepatic function severe dysfunction use about 30% of the normal dose) or impaired renal function, and patients ould be monitored for abnormal prolongation of the PR interval or other signs of overdosage. rapamil may decrease neuromuscular transmission in patients with Duchenne's muscular strophy and may prolong recovery from the neuromuscular blocking agent vecuronium. It may necessary to decrease verapamil dosage in patients with attenuated neuromuscular transmis-n. Combined therapy with beta-adrenergic blockers and verapamil may result in additive gative effects on heart rate, atrioventricular conduction and/or cardiac contractility; there have en reports of excessive bradycardia and AV block, including complete heart block. The risks such combined therapy may outweigh the benefits. The combination should be used only th caution and close monitoring. Decreased metoprolol and propranolol clearance may occur en either drug is administered concomitantly with verapamil. A variable effect has been seen th combined use of atenolol. Chronic verapamil treatment can increase serum digoxin levels 50% to 75% during the first week of therapy, which can result in digitalis toxicity. In patients th hepatic cirrhosis, verapamil may reduce total body clearance and extrarenal clearance of itoxin. The digoxin dose should be reduced when verapamil is given, and the patient carefully nitored. Verapamil will usually have an additive effect in patients receiving blood-pressure-vering agents. Disopyramide should not be given within 48 hours before or 24 hours after rapamil administration. Concomitant use of flecainide and verapamil may have additive effects myocardial contractility, AV conduction, and repolarization. Combined verapamil and quinidine erapy in patients with hypertrophic cardiomyopathy should be avoided, since significant potension may result. Concomitant use of lithium and verapamil may result in a lowering of um lithium levels or increased sensitivity to lithium. Patients receiving both drugs must be nitored carefully. Verapamil may increase carbamazepine concentrations during combined use. ampin may reduce verapamil bioavailability. Phenobarbital may increase verapamil clearance. rapamil may increase serum levels of cyclosporin. Verapamil may inhibit the clearance and rease the plasma levels of theophylline. Concomitant use of inhalation anesthetics and calcium agonists needs careful titration to avoid excessive cardiovascular depression. Verapamil may tentiate the activity of neuromuscular blocking agents (curare-like and depolarizing); dosage luction may be required. Adequate animal carcinogenicity studies have not been performed. e study in rats did not suggest a tumorigenic potential, and verapamil was not mutagenic in Ames test. Pregnancy Category C. There are no adequate and well-controlled studies in gnant women. This drug should be used during pregnancy, labor, and delivery only if clearly eded. Verapamil is excreted in breast milk; therefore, nursing should be discontinued during apamil use.

verse Reactions: Constipation (7.3%), dizziness (3.3%), nausea (2.7%), hypotension (2.5%), adache (2.2%), edema (1.9%), CHF, pulmonary edema (1.8%), fatigue (1.7%), dyspnea (1.4%), dycardia: HR < 50/min (1.4%), AV block: total 1°,2°,3° (1.2%), 2° and 3° (0.8%), rash 2%), flushing (0.6%), elevated liver enzymes, reversible non-obstructive paralytic ileus. The owing reactions, reported in 1.0% or less of patients, occurred under conditions where a sal relationship is uncertain: angina pectoris, atrioventricular dissociation, chest pain, claudi-ion, myocardial infarction, palpitations, purpura (vasculitis), syncope, diarrhea, dry mouth, strointestinal distress, gingival hyperplasia, ecchymosis or bruising, cerebrovascular accident, nfusion, equilibrium disorders, insomnia, muscle cramps, paresthesia, psychotic symptoms, kiness, somnolence, arthralgia and rash, exanthema, hair loss, hyperkeratosis, macules, eating, urticaria, Stevens-Johnson syndrome, erythema multiforme, blurred vision, gyneco-stia, galactorrhea/hyperprolactinemia, increased urination, spotty menstruation, impotence.

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Continuing Medical Education

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ARIZONA

The following list of continuing medical education programs in Arizona is compiled by the Arizona Medical Association. All courses listed have been certified as meeting the criteria for Category I of the ArMA CME Certificate and the AMA Physicians Recognition Award. To list Category I continuing medical education programs, please send information to Arizona Medical Association, 810 West Bethany Home Road, Phoenix, AZ 85013; or phone (602) 246-8901.

Brochures and registration forms are available from the contact person or organization sponsoring the program.

October 17-18—**Hospital Accreditation Survey Preparation.** Joint Commission on the Accreditation of Health Care Organizations, Phoenix. Thurs-Fri. Contact: Kyle Dooley Kinder, ArHA, (602) 968-1083.

October 17-21—**The Spine: Current Concepts of Diagnosis and Treatment.** Jefferson Medical College at Scottsdale Princess Resort, Scottsdale. Thur-Mon. Contact: (619) 692-9115.

October 18-19—**Therapeutics Update.** University of Arizona College of Medicine at Los Abrigados Resort, Sedona. Thurs-Fri. Contact: (602) 626-7832.

October 20-24—**Western Orthopaedic Association—55th Annual Meeting.** Westin La Paloma Resort, Tucson. Sun-Thurs. Contact: H. Martin, (415) 671-2164.

October 25-26—**Geriatrics: Dilemmas and Solutions.** Sun Health Corporation at the Arizona Golf Resort and Conference Center. Fri-Sat. Contact: Marian Richardson, (602) 974-4212.

November 1-2—**Hematology and Oncology for the Practicing Physician.** Mayo Clinic-Scottsdale at the Orange Tree Golf Resort, Scottsdale. Fri-Sat. Contact: Trish Gean, Mayo Clinic-Scottsdale.

November 1-2—**Spinal Surgery Seminar.** University of Arizona College of Medicine at Westin La Paloma Resort, Tucson. Fri-Sat. Contact: U of A.

November 2—**Anxiety Disorders: Integrating Psychopharmacology and Psychodynamic Therapy.** The Menninger Clinic at Camelback Inn, Scottsdale. Sat. Contact: Brenda Vink, (800) 288-7377.

November 8-9—**Annual Southwestern Poison Symposium.** University of Arizona College of Medicine at Doubletree Hotel, Tucson. Fri-Sat. Contact: U of A.

November 8-9—**American College of Physicians, Arizona Chapter.** American College of Physicians at Ventana Canyon, Tucson. Fri-Sat. Contact: (800) 523-1546, ext 2723.

November 14-16—**Fourth Annual Spine Workshop.** Barrow's Neurological Institute, St Joseph's Hospital and Medical Center at Marriott's Mountain Shadows Resort, Scottsdale. Wed-Fri. Contact: Toby Anchie, (602) 285-3178 or (800) BARROW-1.

November 15-16—**Pediatric Genetics and Dermatology: A Practical Approach.** University of Arizona College of Medicine at Hotel Park Tucson. Fri-Sat. Contact: (602) 626-7832.

November 15-16—**4th Annual Techniques in Gynecological Surgery.** Mayo Clinic-Scottsdale at the Scottsdale Plaza Resort, Scottsdale. Fri-Sat. Contact: Trish Gean, Mayo Clinic-Scottsdale.

November 15-17—**The Advanced Medical Staff Seminar.** Joint Commission on the Accreditation of Health Care Organizations, Phoenix. Fri-Sun. Contact: Kyle Dooley Kinder, ArHA, (602) 968-1083.

November 22—**Update on Arthritis.** University of Arizona College of Medicine at the Sheraton Conquistador, Tucson. Fri. Contact: U of A.

November 24-27—**8th Annual "State of the Art in Total Joint Replacement."** Harrington Arthritis Research Center, St Luke's Hospital at the Scottsdale Princess Resort, Scottsdale. Sun-Wed. Contact: Nancy Neroni, (602) 254-0377.

CONTACT INFORMATION

ArMA—Contact: Arizona Medical Association, 810 W Bethany Home Rd, Phoenix, AZ 85013. (602) 246-8901.

Mayo Clinic-Scottsdale—Contact: Jodi Lee Smith, Postgraduate Courses, Mayo Clinic-Scottsdale, (602) 391-8300.

U of A—Contact: University of Arizona College of Medicine, Arizona Health Sciences Center, Tucson, AZ 85724. (602) 626-7832.

CALIFORNIA, HAWAII, AND NEVADA

This listing of continuing education programs in California, Hawaii, and Nevada is supplied by the Committee on Continuing Medical Education of the California Medical Association. All courses and meetings listed have been approved for Category I credit toward the CMA Certificate in Continuing Medical Education. To have accredited courses listed here, please send information at least two months in advance to Department of Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690; or phone (415) 541-0900. For more information on accreditation or certification, please write to the above address.

ALLERGY

February 6-8—**Allergy Diagnosis.** UCSD at La Jolla Village Inn. Thurs-Sat. 20 hrs. $290. Contact: Janice Turner, PO Box 2586, La Jolla 92038. (619) 459-1564.

March 27-28—**Asthma and Allergy in the 1990s.** Medical Education Resources at Wyndham Hotel, Palm Springs. Fri-Sat. Contact: MER, 1500 W Canal Ct, Ste 500, Littleton, CO 80120. (800) 421-3756.

ANESTHESIOLOGY

November 3-9—**Hawaiian Seminar on Clinical Anesthesia.** California Society of Anesthesiologists at Hyatt Regency Hotel, Poipu Beach, Kauai, Hawaii. 1 week. 20 hrs. $415. Contact: CSA, 1065 E Hillsdale Blvd, Ste 410, Foster City 94404. (800) 345-3691.

November 8-10—**Anesthesiology Update: 1991.** UCD at Monterey Plaza Hotel, Monterey. Fri-Sun. 14 hrs. $370. Contact: UCD.

January 9-12—**UCSD Anesthesia Update: 1992.** UCSD at Hotel del Coronado, San Diego. Thurs-Sun. Contact: UCSD.

January 19-21—**Second America-Japan Anesthesia Congress.** International Anesthesia Research Society at Sheraton Waikiki Hotel, Honolulu, Hawaii. Sun-Tue. 14 hrs. $250. Contact: Vicky Larsen, University of Utah School of Medicine, 50 North Medical Drive, Salt Lake City, UT 84132. (801) 581-6115.

January 19-24—**Hawaiian Seminar on Clinical Anesthesia.** California Society of Anesthesiologists at Westin Maui Hotel, Kaanapali Beach, Maui, Hawaii. Sun-Fri. 20 hrs. Contact: California Society of Anesthesiologists, 1065 E Hillsdale Blvd, #410, Foster City 94404. (800) 345-3691.

January 24-26—**30th Clinical Conference in Pediatric Anesthesiology.** Children's Hospital of Los Angeles at Stouffer Concourse Hotel. Fri-Sun. 15 hrs. Contact: Katherine Barky, MD, PO Box 54700, Los Angeles 90054. (213) 669-2262.

March 13-17—**66th Congress of the International Anesthesia Research Society.** International Anesthesia Research Society at San Francisco Hilton & Towers. Fri-Tues. Contact: Anne Maggiore, IARS, 2 Summit Park Dr, Ste 140, Cleveland, OH 44131. (216) 642-1124.

March 21-22—**Postgraduate Assembly.** Los Angeles County Society of Anesthesiologists at Sheraton Universal Hotel, Universal City. Sat-Sun. Contact: Michael Carlson, 1903 Redondo Ave, Long Beach 90804. (213) 597-2661.

March 21-26—**20th Obstetric Anesthesia Conference.** Ohio State University Hospitals at Sheraton Waikiki Hotel, Honolulu, Hawaii. Sat-Thurs. Contact: Arlene Rogers, 410 W 10th Ave, Columbus, OH 43210. (614) 293-8487.

CARDIOLOGY

October 18-19—**Coronary Heart Disease Update.** Medical Education Resources at Parc Fifty Hotel, San Francisco. Fri-Sat. Contact: Karen DeBont, MER, 1500 W Canal Ct, Ste 500, Littleton, CO 80120-4528. (800) 421-3756.

October 18-19—**Cardiology for the Clinician.** Memorial/UCI Center for Health Education. Fri-Sat. Contact: UCI.

(Continued on Page 350)

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(Continued from Page 340)

421 A Lethal Leviathan—*Vibrio vulnificus*

J. MICHAEL JANDA, PhD

Dr Janda is with the Microbial Diseases Laboratory, California Department of Health Services, Berkeley.

423 Molecular Advances in Retinitis Pigmentosa

RICHARD G. WELEBER, MD, and WILLIAM H. MURPHEY, PhD

Dr Weleber is Professor of Ophthalmology and Medical Genetics, Oregon Health Sciences University, and Dr Murphey is Coordinator, Oregon Reginitis Pigmentosa Center, Portland, Oregon.

424 Niacin—The Long and the Short of It

MARY J. MALLOY, MD; PHILIP H. FROST, MD; and JOHN P. KANE, MD, PhD

From the Cardiovascular Research Institute, Department of Medicine, University of California, San Francisco, School of Medicine.

426 Preceptorships in the 21st Century—The Return of the Apprentice

F. MARIAN BISHOP, PhD, MSPH, and NEAL A. WHITMAN, MPA, EdD

From the Department of Family and Preventive Medicine, University of Utah School of Medicine, Salt Lake City.

CORRESPONDENCE

428 Public Interest in Human Growth Hormone Therapy

PAUL S. SALVA, MD, PhD, and GEORGE E. BACON, MD

428 Tort Reform Works

JOSEPH D. SABELLA, MD

429 Medical Tourists

DAVID BISHAI, MD, MPH
FRED WURLITZER, MD, Responds

430 The Menace of Alcohol

EBEN ALEXANDER, Jr, MD
KENNETH W. KIZER, MD, MPH, Responds

430 Perspectives on 'Impairment'

SHELDON L. WAGNER, MD

431 The Value of Defiance

HOWARD M. GRINDLINGER, MD

OTHER FEATURES

333 Subscription Information

342 Continuing Medical Education Activities in Arizona; California, Hawaii, and Nevada; Colorado; Idaho; New Mexico; Utah; Washington; Wyoming

361 Instructions for Authors

433 Classified Advertising

444 Western State Medical Associations' Meetings

Poems: 369, 432

★ Official Journal of the Alaska State Medical Association, the Arizona Medical Association, the California Medical Association, the Denver Medical Society, the Idaho Medical Association, the Nevada State Medical Association, the New Mexico Medical Society, the Utah Medical Association, the Washington State Medical Association, and the Wyoming Medical Society.

★ Affiliated Clinical Investigation Societies: the Western Association of Physicians; the Western Society for Clinical Investigation; the Western Section, American Federation for Clinical Research; the Western Society for Pediatric Research; the Western Region, Society for Investigative Dermatology.

The EXCEL Study:
48 weeks, 8,245 patients,
362 medical centers,
in the largest-ever U.S.
randomized, double-blind,
placebo-controlled
trial of patients with primary
hypercholesterolemia

---

the results are in...

For a Brief Summary of Prescribing Information,
please see the last page of this advertisement.

Bradford, R.H. et al.: Expanded clinical evaluation of lovastatin (EXCEL) study results: I. Efficacy in modifying plasma lipoproteins and adverse event profile in 8,245 patients with moderate hypercholesterolemia, *Archives of Internal Medicine,* January 1991.

Lovastatin lowere
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MEVACOR® (Lovastatin, MSD) is contraindicated in patients who are hypersensitive to any component of the medication; in patients with active liver disease or unexplained persistent transaminase elevations; in pregnant or lactating patients; and in women of childbearing age, except when such patients are highly unlikely to conceive.

For complete details on MEVACOR, including cautionary information regarding myopathy, drug interactions, and liver enzyme monitoring, please refer to the Prescribing Information.

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*Mean percent changes from baseline (n=6,582)
**Triglyceride values are median changes.
Dosage ranged from 20 mg q.p.m. to 40 mg b.i.d.

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DL cholesterol* 24-40%

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iglycerides** 10-19%

DL cholesterol* 6.6-9.5%

For many patients with primary hypercholesterolemia (Types IIa and IIb), when diet and other nondrug therapies are inadequate

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Active liver disease or unexplained persistent elevations of serum transaminases

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Atherosclerosis is a chronic process and the discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. Moreover, cholesterol and other products of the cholesterol biosynthesis pathway are essential components for fetal development, including synthesis of steroids and cell membranes. Because of the ability of inhibitors of HMG-CoA reductase such as MEVACOR® (Lovastatin, MSD) to decrease the synthesis of cholesterol and possibly other products of the cholesterol biosynthesis pathway, MEVACOR may cause fetal harm when administered to a pregnant woman. Therefore, lovastatin is contraindicated during pregnancy. Lovastatin should be administered to women of childbearing age only when such patients are highly unlikely to conceive. If the patient becomes pregnant while taking this drug, lovastatin should be discontinued and the patient should be apprised of the potential hazard to the fetus.

WARNINGS. *Liver Dysfunction*. **Marked persistent increases (to more than 3 times the upper limit of normal) in serum transaminases occurred in 1.9% of adult patients who received lovastatin for at least one year in clinical trials (see ADVERSE REACTIONS).** When the drug was interrupted or discontinued in these patients, the transaminase levels usually fell slowly to pretreatment levels. The increases usually appeared 3 to 12 months after the start of therapy with lovastatin and were not associated with jaundice or other clinical signs or symptoms. There was no evidence of hypersensitivity. A liver biopsy was done in one of these patients and showed areas of focal hepatitis. In this patient, transaminase levels returned to normal following discontinuation of therapy. Some of these patients had abnormal liver function tests prior to lovastatin therapy and/or consumed substantial quantities of alcohol.

It is recommended that liver function tests be performed before treatment begins, every 4 to 6 weeks during the first 15 months of therapy with lovastatin, and periodically thereafter in all patients. Special attention should be paid to patients who develop elevated serum transaminase levels, and in these patients, measurements should be repeated promptly and then performed more frequently. If the transaminase levels show evidence of progression, particularly if they rise to 3 times the upper limit of normal and are persistent, the drug should be discontinued. Liver biopsy should be considered if elevations are persistent beyond the discontinuation of the drug.

The drug should be used with caution in patients who consume substantial quantities of alcohol and/or have a past history of liver disease. Active liver disease or unexplained transaminase elevations are contraindications to the use of lovastatin.

As with other lipid-lowering agents, moderate (less than 3 times the upper limit of normal) elevations of serum transaminases have been reported following therapy with MEVACOR (see ADVERSE REACTIONS). These changes appeared soon after initiation of therapy with MEVACOR, were often transient, were not accompanied by any symptoms, and interruption of treatment was not required.

Skeletal Muscle. **Rhabdomyolysis has been associated with lovastatin therapy alone, when combined with immunosuppressive therapy including cyclosporine in cardiac transplant patients, and when combined in non-transplant patients with either gemfibrozil or lipid-lowering doses (≥1 g/day) of nicotinic acid. Some of the affected patients had preexisting renal insufficiency, usually as a consequence of long-standing diabetes. Acute renal failure from rhabdomyolysis has been seen more commonly with the lovastatin-gemfibrozil combination and has also been reported in transplant patients receiving lovastatin plus cyclosporine.**

Rhabdomyolysis with or without renal impairment has been reported in seriously ill patients receiving erythromycin concomitantly with lovastatin. Therefore, patients receiving concomitant lovastatin and erythromycin should be carefully monitored.

Fulminant rhabdomyolysis has been seen as early as 3 weeks after initiation of combined therapy with gemfibrozil and lovastatin but may be seen after several months. For these reasons, it is felt that, in most subjects who have had an unsatisfactory lipid response to either drug alone, the possible benefits of combined therapy with lovastatin and gemfibrozil do not outweigh the risks of severe myopathy, rhabdomyolysis, and acute renal failure. While it is not known whether this interaction occurs with fibrates other than gemfibrozil, myopathy and rhabdomyolysis have occasionally been associated with the use of other fibrates alone, including clofibrate. Therefore, the combined use of lovastatin with other fibrates should generally be avoided.

Physicians contemplating combined therapy with lovastatin and lipid-lowering doses of nicotinic acid or with immunosuppressive drugs should carefully weigh the potential benefits and risks and should carefully monitor patients for any signs and symptoms of muscle pain, tenderness, or weakness, particularly during the initial months of therapy and during any periods of upward dosage titration of either drug. Periodic CPK determinations may be considered in such situations, but there is no assurance that such monitoring will prevent the occurrence of severe myopathy. The monitoring of lovastatin drug and metabolite levels may be considered in transplant patients who are treated with immunosuppressives and lovastatin.

Lovastatin therapy should be temporarily withheld or discontinued in any patient with an acute, serious condition suggestive of a myopathy or having a risk factor predisposing to the development of renal failure secondary to rhabdomyolysis, including severe acute infection, hypotension, major surgery, trauma, severe metabolic, endocrine, and electrolyte disorders, and uncontrolled seizures.

Myalgia has been associated with lovastatin therapy. Transient, mildly elevated creatine phosphokinase levels are commonly seen in lovastatin-treated patients. However, in clinical trials, approximately 0.5% of patients developed a myopathy, i.e., myalgia or muscle weakness associated with markedly elevated CPK levels. Myopathy should be considered in any patient with diffuse myalgias, muscle tenderness, or weakness, and/or marked elevation of CPK. Patients should be advised to report promptly unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever. Lovastatin therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected.

Most of the patients who have developed myopathy (including rhabdomyolysis) while taking lovastatin were receiving concomitant therapy with immunosuppressive drugs, gemfibrozil, or lipid-lowering doses of nicotinic acid. In clinical trials, about 30% of patients on concomitant immunosuppressive therapy including cyclosporine developed myopathy; the corresponding percentages for gemfibrozil and niacin were approximately 5% and 2%, respectively.

In 6 patients with cardiac transplants taking immunosuppressive therapy including cyclosporine concomitantly with lovastatin 20 mg/day, the average plasma level of active metabolites derived from lovastatin was elevated to approximately 4 times the expected levels. Because of an apparent relationship between increased plasma levels of active metabolites derived from lovastatin and myopathy, the daily dosage in patients taking immunosuppressants should not exceed 20 mg/day (see DOSAGE AND ADMINISTRATION). Even at this dosage, the benefits and risks of using lovastatin in patients taking immunosuppressants should be carefully considered.

PRECAUTIONS. *General*. Before instituting therapy with MEVACOR® (Lovastatin, MSD), an attempt should be made to control hypercholesterolemia with appropriate diet, exercise, weight reduction in obese patients, and to treat other underlying medical problems (see INDICATIONS AND USAGE).

Lovastatin may elevate creatine phosphokinase and transaminase levels (see ADVERSE REACTIONS). This should be considered in the differential diagnosis of chest pain in a patient on therapy with lovastatin.

Homozygous Familial Hypercholesterolemia. MEVACOR is less effective in patients with the rare homozygous familial hypercholesterolemia, possibly because these patients have no functional LDL receptors. MEVACOR appears to be more likely to raise serum transaminases (see ADVERSE REACTIONS) in these homozygous patients.

Drug Interactions. *Immunosuppressive Drugs, Gemfibrozil, Niacin (Nicotinic Acid), Erythromycin*. See WARNINGS, *Skeletal Muscle*.

Coumarin Anticoagulants. In a clinical trial in warfarin-treated patients designed specifically to observe a potential effect of lovastatin on the prothrombin time, lovastatin in dosages up to 40 mg b.i.d. did not produce any consistent alteration of the anticoagulant action of warfarin. However, since the drug was marketed, clinically evident bleeding and/or increased prothrombin time have been reported in a few patients taking coumarin anticoagulants concomitantly with lovastatin. The causal relationship to lovastatin is unclear. Nevertheless, it is recommended that in patients taking anticoagulants, prothrombin time be determined before starting lovastatin and frequently enough during early therapy to insure that no significant alteration of prothrombin time occurs. Once a stable prothrombin time has been documented, prothrombin times can be monitored at the intervals usually recommended for patients on coumarin anticoagulants. If the dose of lovastatin is changed, the same procedure should be repeated. Lovastatin therapy has not been associated with bleeding or with changes in prothrombin time in patients not taking anticoagulants.

Antipyrine. Antipyrine is a model for drugs metabolized by the microsomal hepatic enzyme system (cytochrome P450 system). Because lovastatin had no effect on the pharmacokinetics of antipyrine, interactions with other drugs metabolized via this mechanism are not expected.

Propranolol. In normal volunteers, there was no clinically significant pharmacokinetic or pharmacodynamic interaction with concomitant administration of single doses of lovastatin and propranolol.

Digoxin. In patients with hypercholesterolemia, concomitant administration of lovastatin and digoxin resulted in no effect on digoxin plasma concentrations.

Other Concomitant Therapy. Although specific interaction studies were not performed, in clinical studies, lovastatin was used concomitantly with beta blockers, calcium channel blockers, diuretics, and nonsteroidal anti-inflammatory drugs (NSAIDs) without evidence of clinically significant adverse interactions.

Carcinogenesis, Mutagenesis, Impairment of Fertility. In a 21-month carcinogenic study in mice, a statistically significant ($p < 0.05$) increase in the incidence of hepatocellular carcinomas and adenomas was observed at doses of 500 mg/kg/day (312 times the maximum recommended human dose) of lovastatin. These changes were not seen in mice given doses of 20 and 100 mg/kg/day (12.5 and 62.5 times the maximum recommended human dose).

A statistically significant increase ($p \leq 0.05$) in the incidence of pulmonary adenomas was seen in female mice receiving 500 mg/kg/day (312 times the maximum recommended human dose); no similar changes were seen in males at any dose or in females receiving 20 or 100 mg/kg/day (12.5 or 62.5 times the maximum recommended human dose). Because the incidence of pulmonary tumors was within the range of untreated animals in studies of similar duration, the relationship of this latter change to treatment is not known.

In addition, an increase in the incidence of papilloma in the non-glandular mucosa of the stomach was observed in mice receiving 100 and 500 mg/kg/day (6.2.5 and 312 times the maximum recommended human dose); no increase was seen at a dosage of 20 mg/kg/day (12.5 times the maximum recommended human dose). The glandular mucosa was not affected. The human stomach contains only glandular mucosa. Importantly, there is a strong association between this change and hyperplasia of the squamous epithelium (acanthosis) in this region; acanthosis is a characteristic change observed in the non-glandular mucosa of rodents treated with HMG-CoA reductase inhibitors and is most probably a result of inhibition of the reductase in this tissue.

Similar squamous epithelium is found in the esophagus and anorectal junction of the mouse and rat; however, no evidence of a similar drug-induced hyperplastic response was observed in these tissues in studies of up to 21 months in the mouse given up to 500 mg/kg/day (312 times the maximum recommended human dose), or in a study of 24 months in the rat given 180 mg/kg/day (112 times the maximum recommended human dose).

In a 24-month carcinogenicity study in rats, there was a positive dose response relationship for hepatocellular carcinogenicity in males (unadjusted $p = 0.025$). However, because the incidence of hepatocellular carcinogenicity observed in male rats in this study is similar to that observed spontaneously in this strain of rat, the implications of this finding are unclear.

Drug-related testicular atrophy, decreased spermatogenesis, spermatocytic degeneration and giant cell formation were seen in dogs starting at 20 mg/kg/day (12.5 times the maximum recommended human dose). The clinical significance of these findings is unclear.

No evidence of mutagenicity was observed in a microbial mutagen test using mutant strains of *Salmonella typhimurium* with or without rat or mouse liver metabolic activation. In addition, no evidence of damage to genetic material was noted in an *in vitro* alkaline elution assay using rat or mouse hepatocytes, a V-79 mammalian cell forward mutation study, an *in vitro* chromosome aberration study in CHO cells, or an *in vivo* chromosomal aberration assay in mouse bone marrow.

No drug-related effects on fertility were found in studies with rats.

Pregnancy. Pregnancy Category X. See CONTRAINDICATIONS.

Lovastatin has been shown to produce skeletal malformations in the rat fetus at doses of 800 mg/kg/day (500 times the maximum recommended human dose). At similar doses in mice, an increase in skeletal malformations was observed. These individual changes are within the range of those observed spontaneously in this strain of mouse. No drug-induced changes were seen in either species at doses of up to 80 mg/kg/day (50 times the maximum recommended human dose). No evidence of malformations was noted in rabbits at up to 15 mg/kg/day (highest tolerated dose – about 9 times the maximum recommended human dose). There are no data in pregnant women.

Nursing Mothers. Studies in rats have shown that lovastatin is excreted in the milk. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from MEVACOR, women taking lovastatin should not nurse their infants (see CONTRAINDICATIONS).

Pediatric Use. Safety and effectiveness in children have not been established. Because children are not likely to benefit from cholesterol lowering for at least a decade and because experience with this drug is limited (no studies in subjects below the age of 20 years), treatment of children with lovastatin is not recommended at this time.

ADVERSE REACTIONS. MEVACOR is generally well tolerated, adverse reactions usually have been mild and transient. Less than 1% of patients were discontinued from controlled clinical studies due to adverse experiences attributable to MEVACOR. About 2% of patients were discontinued from all studies (controlled and uncontrolled) due to adverse experiences attributable to MEVACOR, about one-third of these patients were discontinued due to increases in serum transaminases.

Clinical Adverse Experiences. Adverse experiences reported in patients treated with MEVACOR® (Lovastatin, MSD) in controlled clinical studies are shown in the table below.

	MEVACOR (N=613) %	Placebo (N=82) %	Cholestyramine (N=88) %	Probucol (N=9[illegible]) %
Gastrointestinal				
Constipation	4.9		34.1	2.1
Diarrhea	5.5	4.9	8.0	10.3
Dyspepsia	3.9		13.6	3.1
Flatus	6.4	2.4	21.6	2.1
Abdominal pain/cramps	5.7	2.4	5.7	5.2
Heartburn	1.6		8.0	—
Nausea	4.7	3.7	9.1	6.2
Musculoskeletal				
Muscle cramps	1.1	—	1.1	—
Myalgia	2.4	1.2	—	—
Nervous System/Psychiatric				
Dizziness	2.0	1.2	—	1.0
Headache	9.3	4.9	4.5	8.2
Skin				
Rash/pruritus	5.2		4.5	—
Special Senses				
Blurred vision	1.5		1.1	3.1
Dysgeusia	0.8	—	1.1	—

Laboratory Tests. Marked persistent increases of serum transaminases have been noted (see WARNINGS).

About 11% of patients had elevations of creatine phosphokinase (CPK) levels of at least twice the normal value on one or more occasions. The corresponding values for the control agents were cholestyramine, 9%, and probucol, 2%. This was attributable to the noncardiac fraction of CPK. Large increases in CPK have sometimes been reported (see WARNINGS, *Skeletal Muscle*).

Concomitant Therapy. In controlled clinical studies in which lovastatin was administered concomitantly with cholestyramine, no adverse reactions peculiar to this concomitant treatment were observed. The adverse reactions that occurred were limited to those reported previously with lovastatin or cholestyramine. Other lipid-lowering agents were not administered concomitantly with lovastatin during controlled clinical studies. In uncontrolled clinical studies, most of the patients who have developed myopathy were receiving concomitant therapy with immunosuppressive drugs, gemfibrozil, or niacin (nicotinic acid) (see WARNINGS, *Skeletal Muscle*).

Uncontrolled Clinical Studies. The adverse experiences observed in uncontrolled studies were similar to those seen in controlled clinical studies. Abnormal liver function tests were observed at a higher incidence than in the controlled studies (see WARNINGS, *Liver Dysfunction*). Myopathy (myalgia with marked CPK elevations) was reported in approximately 0.5% of patients (see WARNINGS, *Skeletal Muscle*).

Causal Relationship Unclear. *Nervous System*. Peripheral neuropathy has been reported; the relationship to lovastatin is uncertain. Visual evoked response, nerve conduction measurements, and electromyography in over 30 patients showed no evidence of neurotoxic effects of lovastatin.

Eye. Lens opacities (see CLINICAL PHARMACOLOGY, *Clinical Studies*).

Post-marketing Experience. Additional adverse experiences occurring since the drug was marketed are listed below.

Clinical Adverse Experiences

Gastrointestinal. Hepatitis, cholestatic jaundice, anorexia, vomiting.

Hypersensitivity Reactions. An apparent hypersensitivity syndrome has been reported rarely which has included one or more of the following features: anaphylaxis, angioedema, lupus-like syndrome, polymyalgia rheumatica, vasculitis, thrombocytopenia, leukopenia, hemolytic anemia, positive ANA, ESR increase, arthritis, arthralgia, urticaria, asthenia, photosensitivity, fever, chills, flushing, malaise, and dyspnea.

Nervous System/Psychiatric. Psychic disturbances, including anxiety, paresthesia.

Skin. Erythema multiforme, including Stevens-Johnson syndrome, toxic epidermal necrolysis.

Causal Relationship Unknown

Eye. Progression of cataracts (lens opacities).

Gastrointestinal. Pancreatitis, stomatitis.

Skin. Alopecia.

Nervous System/Psychiatric. Depression, insomnia.

Metabolic. Edema.

Clinical Laboratory Test Findings

Liver Function Tests. Liver function test abnormalities, including elevated alkaline phosphatase and bilirubin.

Thyroid Function Tests. Rare reports of thyroid function test abnormalities in patients taking concomitant thyroxine.

OVERDOSAGE. The oral LD_{50} of MEVACOR in mice is 20 g/kg.

Five healthy human volunteers have received up to 200 mg of lovastatin as a single dose without clinically significant adverse experiences. A few cases of accidental overdosage have been reported; no patients had any specific symptoms, and all patients recovered without sequelae. The maximum dose taken was 5 to 6 g.

Until further experience is obtained, no specific treatment of overdosage with MEVACOR can be recommended.

The dialyzability of lovastatin and its metabolites in man is not known at present.

DOSAGE AND ADMINISTRATION. The patient should be placed on a standard cholesterol-lowering diet before receiving MEVACOR and should continue on this diet during treatment with MEVACOR. MEVACOR should be given with meals.

The recommended starting dose is 20 mg once a day given with the evening meal. The recommended dosing range is 20 to 80 mg/day in single or divided doses; the maximum recommended dose is 80 mg/day. Adjustments of dosage should be made at intervals of 4 weeks or more. Doses should be individualized according to the patient's response (see Tables I to IV under CLINICAL PHARMACOLOGY, *Clinical Studies* for dose-response results).

For those patients with severely elevated serum cholesterol levels (i.e., >300 mg/dL [7.8 mmol/L] on diet), MEVACOR may be initiated at 40 mg/day.

In patients taking immunosuppressive drugs concomitantly with lovastatin (see WARNINGS, *Skeletal Muscle*), therapy should begin with 10 mg of MEVACOR and should not exceed 20 mg/day.

Cholesterol levels should be monitored periodically and consideration should be given to reducing the dosage of MEVACOR if cholesterol levels fall below the targeted range.

Concomitant Therapy. Preliminary evidence suggests that the cholesterol-lowering effects of lovastatin and the bile acid sequestrant cholestyramine are additive.

Dosage in Patients with Renal Insufficiency. In patients with severe renal insufficiency (creatinine clearance 30 mL/min), dosage increases above 20 mg/day should be carefully considered and, if deemed necessary, implemented cautiously (see CLINICAL PHARMACOLOGY and WARNINGS, *Skeletal Muscle*).

MS
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SHAR
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For more detailed information, consult your MSD Representative or s
Prescribing Information. Merck Sharp & Dohme, Division of Merck Co., Inc., West Point, PA 19486 J0MC49R2(5

ABSTRACTS OCTOBER 1991

(Murdock MA, Waxman K: Helmet use improves outcomes after motorcycle accidents. West J Med 1991 Oct; 155:370-372)

To determine the effects of motorcycle helmet use on the outcome of patients admitted to a Level I trauma center, we studied patient outcomes and demographic and epidemiologic variables of 474 patients injured in motorcycle collisions and treated at such a center over a 45-month period. Of those involved in a motorcycle collision, 50% were not wearing a helmet, 23% were wearing a helmet, and in 27% helmet use was unknown. Those who were wearing a helmet had fewer and less severe head and facial injuries, required fewer days on a ventilator, and sustained no serious neck injuries; fewer patients who wore helmets were discharged with disability, and hospital charges were lower. These data support the need for both increased public education regarding helmet use and mandatory helmet use legislation.

TRAUMA
MOTORCYCLE ACCIDENT
HEAD INJURIES
HELMET USE
NECK INJURIES

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Three copies of this abstract are provided to help you in filing and cross-referencing research articles.

CONTINUING MEDICAL EDUCATION

(Continued from Page 342)

November 2—**Cardiac Risk Reduction Conference.** UCD at Radisson Hotel, Sacramento. Sat. Contact: UCD.

November 8-9—**Coronary Interventions: 1991.** Scripps Clinic and Research Foundation at La Jolla Marriott Hotel. Fri-Sat. 14 hrs. $550. Contact: Susan Buntjer, 400S, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

November 9—**Advances in Cardiac Imaging.** Memorial/UCI Center for Health Education at Marriott, Irvine. Sat. Contact: UCI.

November 15-16—**The Cardiac Patient.** Memorial/UCI Center for Health Education at Marriott, Newport Beach. Fri-Sat. Contact: UCI.

December 7—**9th Annual International Pulmonary Symposium.** Memorial/UCI Center for Health Education. Sat. Contact: UCI.

February 14-16—**Arrhythmias: Interpretation, Diagnosis and Management.** Medical Education Resources at Disneyland Hotel, Anaheim. Fri-Sun. Contact: MER, 1500 W Canal Ct, Ste 500, Littleton, CO 80120. (800) 421-3756.

March 20-21—**Cardiac Diagnostic Methods & Risk Management.** Medical Education Resources at Caesars Palace, Las Vegas, Nevada. Fri-Sat. Contact: MER, 1500 W Canal Ct, Ste 500, Littleton, CO 80120. (800) 421-3756.

CRITICAL CARE

October 17-19—**Traumatic Brain Injury.** UCD at Radisson Hotel, Sacramento. Thurs-Sat. 23 hrs. $435. Contact: UCD.

October 17-19—**10th Annual Recent Advances in Pulmonary and Critical Care Medicine.** UCSF at Sheraton Palace Hotel, San Francisco. Thurs-Sat. 15 hrs. $395. Contact: UCSF.

October 19—**Norman Sharrer Symposium: Critical Care Revisited.** Kaweah Delta District Hospital at Radisson Hotel, Visalia. Sat. 6 hrs. $30. Contact: Brooke Mack, (209) 625-7308.

KEY TO ABBREVIATIONS

CMA California Medical Association
Contact: Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690. (415) 541-0900.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Herbert M. Thomas, MD, MPH, Director of CME, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th St, Los Angeles 90059. (213) 603-3183.

LLU: Loma Linda University
Contact: James J. Couperus, MD, Associate Dean for Educational Affairs, Loma Linda University School of Medicine, Loma Linda 92350.

PMC: Pacific Medical Center
Contact: Continuing Education, Pacific Medical Center, PO Box 7999, San Francisco 94120. (415) 563-4321, ext 2761.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Medical School Office Building, Suite X-365, Stanford 94305-6114 (415) 723-5594.

UCD University of California, Davis
Contact: Ruth Feryok, Director, Office of Continuing Medical Education, University of California, Davis, School of Medicine, 2701 Stockton Blvd, Sacramento 95817. (916) 734-5390.

UCI: University of California, Irvine
Contact: Melvin I. Marks, MD, Director, Memorial/UCI Center for Health Education, Long Beach Memorial Medical Center, 2801 Atlantic Ave, PO Box 1428, Long Beach, California 90801-1428 (213) 595-3811

UCLA University of California, Los Angeles Extension
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, PO Box 24902, UCLA, Los Angeles 90024 (213) 825-8423.

UCSD: University of California, San Diego
Contact: Office of Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (619) 534-3940.

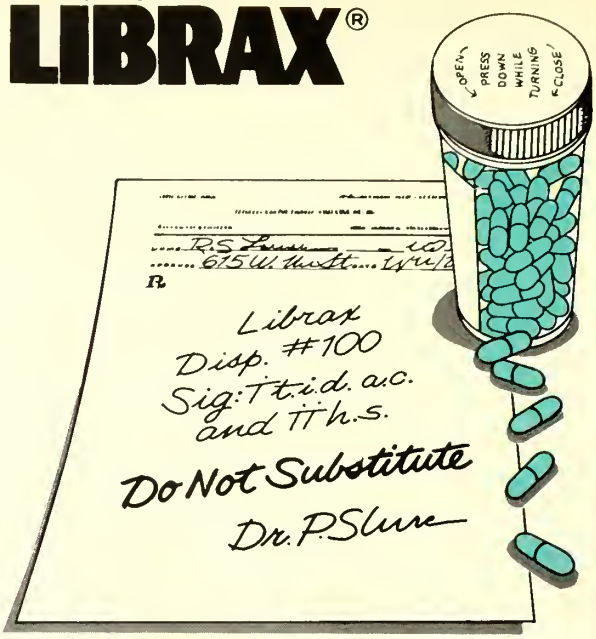
UCSF: University of California, San Francisco
Contact: Janet Johnson, Administrative Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 476-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 1975 Zonal Ave, KAM314, Los Angeles 90033. (213) 224-7051.

(Continued on Page 352)

Specify Adjunctive

LIBRAX®



Each capsule contains 5 mg chlordiazepoxide HCl and 2.5 mg clidinium bromide.

Please consult complete prescribing information, a summary of which follows:

Indications: Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:
"Possibly" effective: as adjunctive therapy in the treatment of peptic ulcer and in the treatment of the irritable bowel syndrome (irritable colon, spastic colon, mucous colitis) and acute enterocolitis.
Final classification of the less-than-effective indications requires further investigation.

Contraindications: Glaucoma; prostatic hypertrophy, benign bladder neck obstruction; hypersensitivity to chlordiazepoxide HCl and/or clidinium Br.
Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants, and against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving).
Usage in Pregnancy: **Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy. Advise patients to discuss therapy if they intend to or do become pregnant.**
As with all anticholinergics, inhibition of lactation may occur.
Withdrawal symptoms of the barbiturate type have occurred after discontinuation of benzodiazepines (see Drug Abuse and Dependence).
Precautions: In elderly and debilitated, limit dosage to smallest effective amount to preclude ataxia, oversedation, confusion (no more than 2 capsules/day initially; increase gradually as needed and tolerated). Though generally not recommended, if combination therapy with other psychotropics seems indicated, carefully consider pharmacology of agents, particularly potentiating drugs such as MAO inhibitors, phenothiazines. Observe usual precautions in presence of impaired renal or hepatic function. Paradoxical reactions reported in psychiatric patients. Employ usual precautions in treating anxiety states with evidence of impending depression; suicidal tendencies may be present and protective measures necessary. Variable effects on blood coagulation reported very rarely in patients receiving the drug and oral anticoagulants; causal relationship not established. Inform patients to consult physician before increasing dose or abruptly discontinuing this drug.
Adverse Reactions: No side effects or manifestations not seen with either compound alone reported with Librax. When chlordiazepoxide HCl is used alone, drowsiness, ataxia, confusion may occur, especially in elderly and debilitated; avoidable in most cases by proper dosage adjustment, but also occasionally observed at lower dosage ranges. Syncope reported in a few instances. Also encountered: isolated instances of skin eruptions, edema, minor menstrual irregularities, nausea and constipation, extrapyramidal symptoms, increased and decreased libido—all infrequent, generally controlled with dosage reduction; changes in EEG patterns may appear during and after treatment; blood dyscrasias (including agranulocytosis), jaundice, hepatic dysfunction reported occasionally with chlordiazepoxide HCl, making periodic blood counts and liver function tests advisable during protracted therapy. Adverse effects reported with Librax typical of anticholinergic agents, *i.e.*, dryness of mouth, blurring of vision, urinary hesitancy, constipation. Constipation has occurred most often when Librax therapy is combined with other spasmolytics and/or low residue diets.
Drug Abuse and Dependence: Withdrawal symptoms similar to those noted with barbiturates and alcohol have occurred following abrupt discontinuance of chlordiazepoxide; more severe seen after excessive doses over extended periods; milder after taking continuously at therapeutic levels for several months. After extended therapy, avoid abrupt discontinuation and taper dosage. Carefully supervise addiction-prone individuals because of predisposition to habituation and dependence.

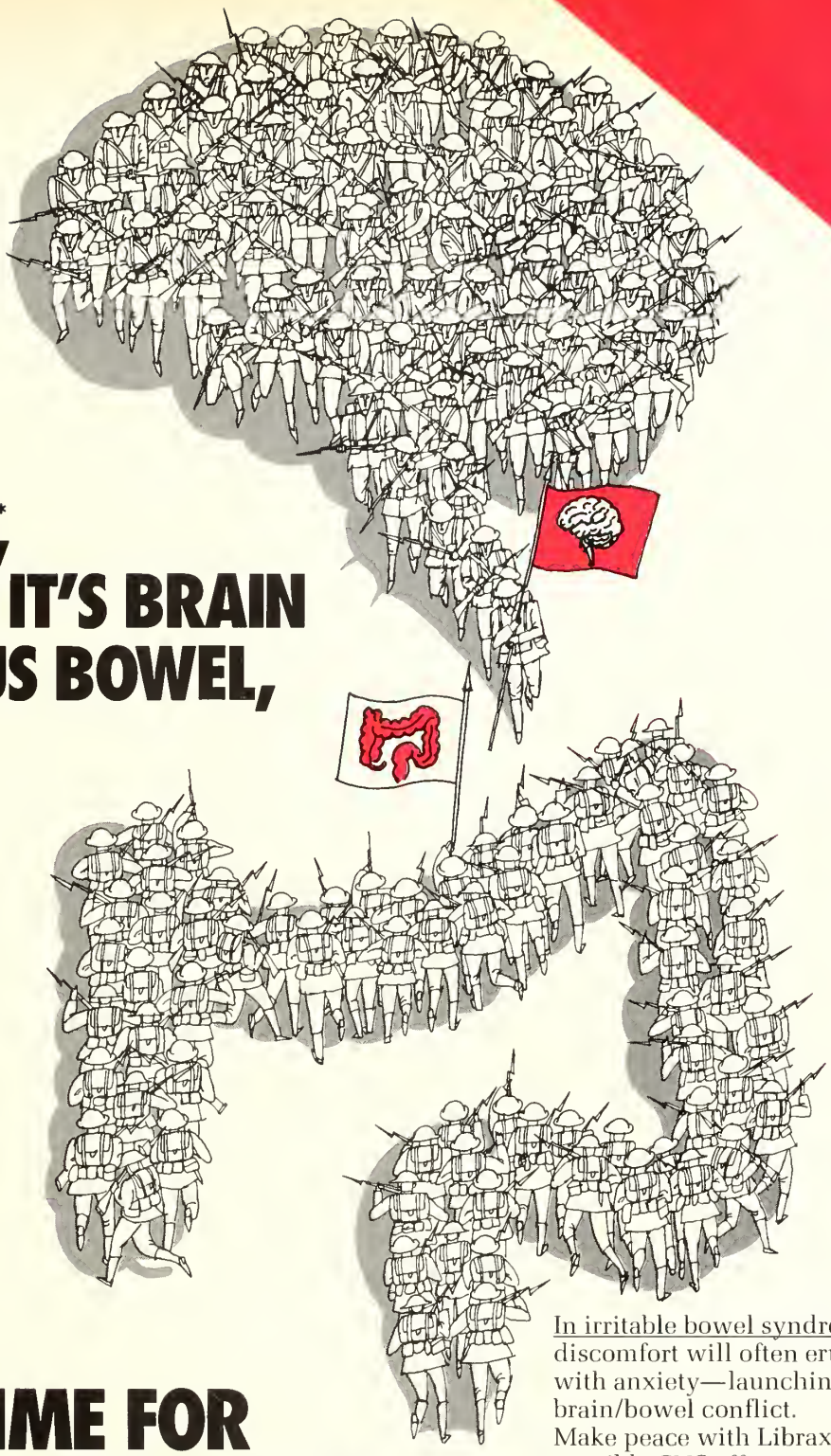
Revised: February 1988

ROCHE **Roche Products**

Roche Products Inc.
Manati, Puerto Rico 00701

Be sure to specify Librax, "Do Not Substitute" or your state's equivalent statement on your prescription.

IN IBS*, WHEN IT'S BRAIN VERSUS BOWEL,



IT'S TIME FOR THE PEACEMAKER.

In irritable bowel syndrome intestinal discomfort will often erupt in tandem with anxiety—launching a cycle of brain/bowel conflict.
Make peace with Librax. Because of possible CNS effects, caution patients about activities requiring complete mental alertness.

*Librax has been evaluated as possibly effective as adjunctive therapy in the treatment of peptic ulcer and IBS.

Specify Adjunctive

LIBRAX®

Each capsule contains 5 mg chlordiazepoxide HCl and 2.5 mg clidinium bromide.

ROCHE

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Please see summary of prescribing information on adjacent page.

(Continued from Page 350)

DERMATOLOGY

November 2—**Dermatology Update: 1991.** Sutter Health at Sacramento Association of Realtors. Sat. Contact: Sutter Health Medical Education, 2800 L St, Sacramento 95816. (800) 777-0231.

November 8-10—**Pediatric Dermatology and Wound Management: Above and Below the Surface.** Children's Hospital Oakland at Monterey Conference Center, Monterey. Fri-Sun. 12 hrs. $300. Contact: Children's Hospital, 747-52nd St, Oakland 94609. (415) 428-3021.

January 17-19—**Practical Dermatology and Dermatologic Office Procedures for the Primary Care Physician.** UCSD at Hyatt Regency, La Jolla. Fri-Sun. 20 hrs. Contact: Jacqueline Shiller, Box 84296, San Diego 92138. (619) 223-2997.

January 31-February 2—**Cutaneous Malignancies: 1992 Skin Cancer Update.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Fri-Sun. 18 hrs. Contact: Susan Buntjer, Scripps Clinic and Research Foundation, 10666 N Torrey Pines Road, La Jolla 92037. (619) 554-8556.

February 27—**Problems of the Aging Skin.** Stanford Medical Center at Palm Springs. Thurs-Sun. Contact: Pamela Bain, R-144, Stanford 94305. (415) 723-7854.

EMERGENCY MEDICINE

October 21-25—**Emergency Medicine Symposia I.** UCSD at La Jolla Marriott. Mon-Fri. Contact: UCSD.

October 28-November 1—**Twentieth Annual Topics in Emergency Medicine.** UCSF at Sheraton Palace Hotel, San Francisco. Mon-Fri. 32 hrs. $510. Contact: UCSF.

November 11-15—**Emergency Medicine Symposia III.** UCSD at San Diego Hilton Beach & Tennis Resort. Mon-Fri. Contact: UCSD.

November 16-17—**Biomechanics of Trauma.** UCSD at San Diego Marriott. Sat-Sun. Contact: UCSD.

December 9-13—**Emergency Medicine Symposia II.** UCSD at Basic Science Building, La Jolla. Mon-Fri. Contact: UCSD.

January 10-11—**California Trauma Conference.** UCD at Hyatt Regency, Sacramento. Fri-Sat. Contact: UCD.

January 13-17—**Emergency Medicine Symposia I.** UCSD at San Diego Hilton Beach & Tennis Resort. Mon-Fri. Contact: UCSD.

February 23-28—**Emergency Medicine.** UCD at Incline Village, Nevada. Sun-Fri. Contact: UCD.

ENDOCRINOLOGY AND METABOLISM

October 18-20—**Obesity Update: Assessment & Treatment.** UCD at Hyatt Regency, Sacramento. Fri-Sun. 18 hrs. $325. Contact: UCD.

October 20-23—**Joint Annual Research Conference on Obesity & Food Intake.** North American Association of the Study of Obesity & Society for Study of Ingestive Behavior at Hyatt Regency, Saramento. Sun-Wed. Contact: UCD.

November 1-2—**Practical Methods in Diabetes.** Memorial/UCI Center for Health Education at Meridien Newport Beach. Fri-Sat. Contact: UCD.

March 4-5—**Advances in Endocrinology and Metabolism.** UCSF at Pan Pacific Hotel, San Francisco. Wed-Thurs. 14.5 hrs. $295. Contact: UCSF.

March 6—**18th Annual Diabetes Symposium.** UCD at Sacramento. Fri. 6 hrs. $140. Contact: UCD.

March 6-7—**Diabetes Update.** UCSF at Pan Pacific Hotel, San Francisco. Fri-Sat. 10 hrs. $245. Contact: UCSF.

FAMILY PRACTICE/PRIMARY CARE

October 18-20—**Office Orthopedics for the Primary Care Physician.** Sharp Memorial Hospital at San Diego Princess at Vacation Village. Fri-Sun. 20 hrs. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

November 15-17—**Family Practice Today & Tomorrow.** UCSD at Sheraton Hotel, San Diego. Fri-Sun. Contact: UCSD.

February 9-15—**UCI Family Practice Refresher Course.** Memorial/UCI Center for Health Education at Marriott Hotel, Newport Beach. Sun-Sat. Contact: UCI.

February 13-15—**Current Concepts in Cancer Management: A Symposium for Primary Care Physicians and Cancer Care Providers.** Hoag Memorial Center at Newport Beach Marriott. Thurs-Sat. $350. Contact: Meeting Management, 5665 Oberlin, Ste 110, San Diego 92121. (619) 453-6222.

February 13-16—**44th Annual Scientific Assembly.** California Academy of Family Physicians at Sheraton Harbor Island Hotel, San Diego. Thurs-Sun. 26 hrs. $275. Contact: Robert Fagan, CAFP, 114 Sansome St, Ste 1305, San Francisco 94104. (415) 394-9121.

February 14-16—**Office Gynecology for the Primary Care Physician.** SDSU at Hyatt Islandia, San Diego. Fri-Sun. 20 hrs. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

February 17-19—**Issues in Men's Health.** SDSU at Hyatt Islandia, San Diego. Mon-Wed. 20 hrs. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

March 25-27—**Annual Review in Family Medicine: Controversies and Challenges in Primary Care.** UCSF. Wed-Fri. 15.5 hrs. Contact: UCSF.

GASTROENTEROLOGY

February 29-March 1—**Endoscopy Update 1992.** Southern California Society for Gastroenterology at Century Plaza Hotel, Los Angeles. Sat-Sun. Contact: Joyce Fried, University of California Brain Research Institute, Los Angeles 90024.

INFECTIOUS DISEASES

February 7-8—**10th Annual Infectious Disease.** UCD. Fri-Sat. Contact: UCD.

INTERNAL MEDICINE

November 1-3—**Diagnosis & Management of Chronic Major Vessel Thromboembolic Pulmonary Hypertension.** UCSD at Sheraton Harbor Island Hotel, San Diego. Sun-Tues. Contact: UCSD.

November 7-9—**San Francisco Otology Update: 1991.** UCSF. Thurs-Sat. 22 hrs. Contact: UCSF.

December 5—**Common Musculoskeletal Problems—Knee.** VA Medical Center Sepulveda. Thurs. 5.5 hrs. Contact: Arun Mehta, MD, VA Med Ctr, (818) 895-9344.

December 6-7—**Clinical Applications of New Advances in Internal Medicine.** UCD at Cancer Center Auditorium. Fri-Sat. 12 hrs. Contact: UCD.

January 30-February 1—**Advanced Nephrology: Nephrology for the Consultant.** UCSD at La Jolla Marriott, San Diego. Thurs-Sat. Contact: UCSD.

February 27-29—**1992 Zimmerman Conference: Progress in Vascular Biology, Hemostasis and Thrombosis.** Scripps Clinic at Sheraton Grande Torrey Pines Hotel, La Jolla. Thurs-Sat. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

March 20-26—**Internal Medicine 1992: A Comprehensive Review.** Sharp Memorial Hospital at Hotel del Coronado. Fri-Thurs. 54 hours. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

NEUROLOGY

October 17-19—**Child Neurology in the Decade of the Brain.** UCSF at Hyatt Regency Hotel, San Francisco. Thurs-Sat. 18.5 hrs. $345. Contact: UCSF.

November 1-2—**Transcranial Doppler and Cerebral Blood Flow Monitoring.** UCLA at Sheraton Miramar Hotel, Santa Monica. Fri-Sat. 12.5 hrs. Contact: UCLA.

January 1-February 1—**15th Annual: Neurology for Non-Neurologists.** UCSD at Omni San Diego Hotel. Thurs-Sat. 21 hrs. $425. Contact: UCSD.

February 13-15—**25th Annual Recent Advances in Neurology.** UCSF at San Francisco. Thurs-Sat. 15 hrs. Contact: UCSF.

OB/GYN

October 23-26—**Trends in OB-GYN Management.** Sharp Memorial Hospital at Hotel del Coronado, San Diego. Wed-Sat. 16 hrs. Contact: Debra L. Gist, 7901 Frost St, San Diego 92123-2788. (619) 541-4530.

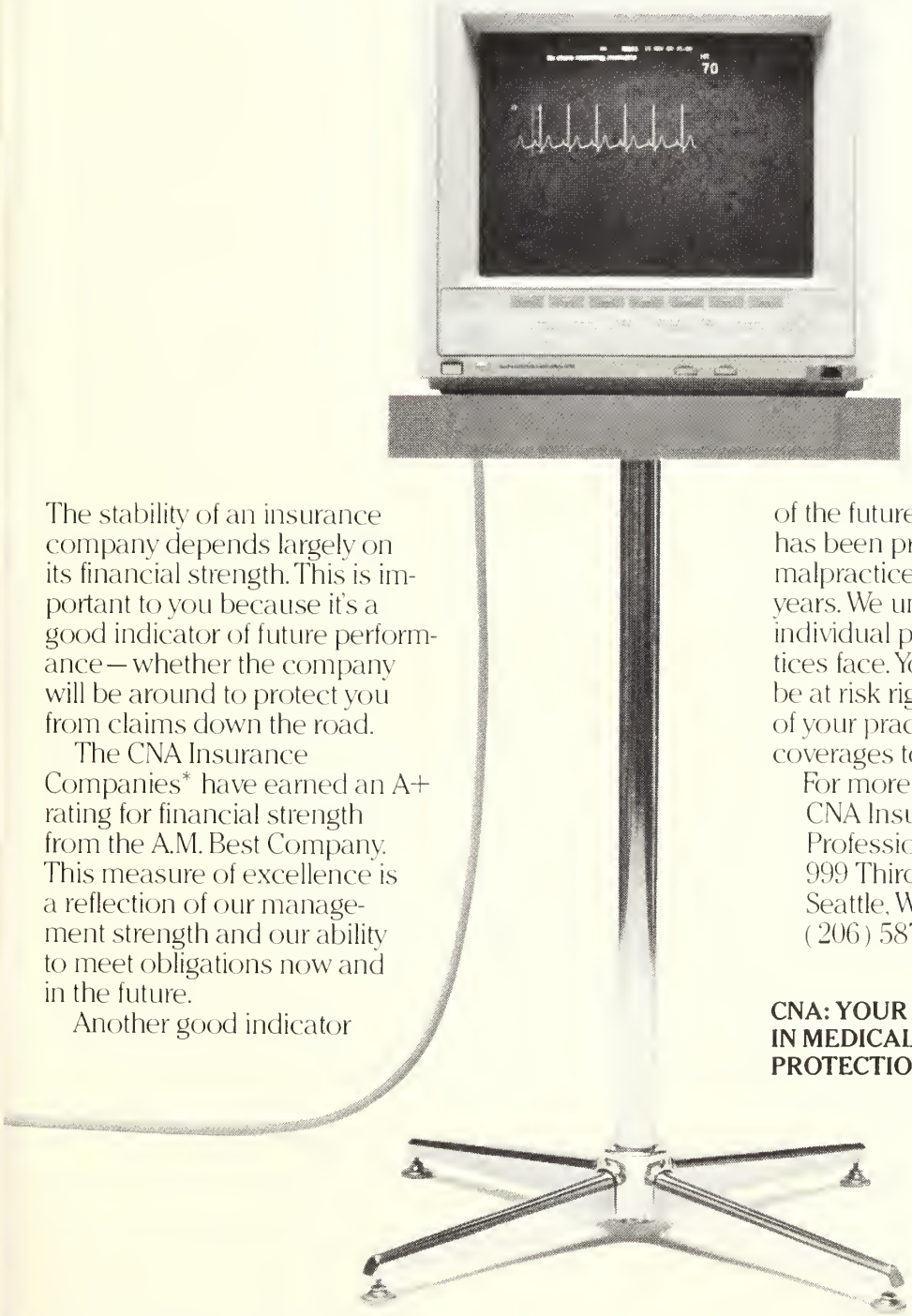
November 8-10—**Current Issues in Perinatal Medicine.** Memorial/UCI at Marriott's Rancho Las Palmas Resort, Palm Springs. Fri-Sun. 15.5 hrs. Contact: UCI.

November 18-23—**14th Annual Review Course in Clinical OB/GYN and Gynecological Histopathology.** Memorial/UCI Center for Health Education at Westin South Coast Plaza, Costa Mesa. Mon-Sat. 44 hrs. Contact: UCI.

January 16-19—**OB/GYN and Ultrasound.** UCSD at Hotel del Coronado, San Diego. Thurs-Sun. 20 hrs. $450. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

(Continued on Page 354)

CNA's financial stability can be vital to the health of your practice.



The stability of an insurance company depends largely on its financial strength. This is important to you because it's a good indicator of future performance—whether the company will be around to protect you from claims down the road.

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CNA
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CONTINUING MEDICAL EDUCATION

(Continued from Page 352)

February 2-6—**Ambulatory Gynecology.** UCD at Hyatt Lake Tahoe, Incline Village, Nevada. Sun-Thurs. Contact: UCD.

February 13-16—**47th Annual Postgraduate Assembly.** OB/GYN Assembly of Southern California at Beverly Hilton, Beverly Hills. Thurs-Sun. 28 hrs. Contact: OB/GYN Assembly, 5820 Wilshire Blvd, #500, Los Angeles 90036. (213) 937-5514.

OCCUPATIONAL/ENVIRONMENTAL

October 21-25—**Sports Medicine Update.** Memorial/UCI Center for Health Education in Hawaii. Mon-Fri. Contact: UCI.

October 21-November 1—**Occupational and Environmental Medicine: Session II.** UCSF at Miyako Hotel, San Francisco. Mon-Fri. 80 hrs. $1200. Contact: UCSF.

October 28-November 1—**Advances in Occupational and Environmental Medicine.** UCSF at Miyako Hotel, San Francisco. Mon-Fri. 40 hrs. $600. Contact: UCSF.

January 27-February 7—**Occupational and Environmental Medicine Series: Session I.** UCSF at Miyako Hotel, San Francisco. Mon-Fri. 80 hrs. $1200. Contact: UCSF.

February 10-14—**Occupational and Environmental Medicine: Session III.** UCSF at Miyako Hotel Japan Center, San Francisco. Mon-Fri. 40 hrs. $600. Contact: UCSF.

February 12-16—**Team Physician Course.** American College of Sports Medicine at Wyndham Hotel, Palm Springs. Wed-Sun. Contact: ACMS, PO Box 1440, Indianapolis, IN 46202-1440. (317) 637-9200.

ONCOLOGY

October 14-20—**17th Annual Lymphoma Course.** Scripps Clinic and Research Foundation, La Jolla. Mon-Fri. 25 hrs. $550. Contact: Laurel Steigerwald, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

October 19—**10th Annual Cancer Symposium: Update & Overview.** Hi Desert Joint Cancer Program at Bally's Hotel, Las Vegas. Sat. $75. Contact: Alice Williams, 18300 Hwy 18, Apple Valley 92307. (619) 242-2311, ext 445.

November 13—**Women and Cancer: Early Detection and Follow-up Care.** Alta Bates-Herrick Hospital at Hospital Auditorium. Wed. 5.5 hrs. $60. Contact: Mary Grim, (415) 540-1420.

November 21-23—**3rd Annual Symposium on Diagnosis and Treatment of Musculoskeletal Tumors.** UCD at Hyatt Regency, Sacramento. Thurs-Sat. 16 hrs. $450. Contact: UCD.

February 17-19—**Clinical Hematology and Oncology: 1992.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Mon-Wed. 18 hrs. $385. Contact: Susan Buntjer, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

OPHTHALMOLOGY

January 31-February 4—**11th Annual Squaw Valley Retina Symposium.** Alta-California Ophthalmological Society at Resort at Squaw Creek, Olympic Valley. Fri-Tues. 16 hrs. Contact: Richard Murray, 2701 Eye St, Sacramento 95816. (916) 442-4975.

ORTHOPEDICS

October 17-18—**4th Annual International Symposium on Custom Prostheses.** Sutter Health at Stanford Court Nob Hill, San Francisco. 20 hrs. $450. Contact: Sutter Health, 2800 L St, Sacramento 95816. (800) 777-0231.

January 23-25—**Orthopaedic Update II: Current Concepts and Advances.** UCSD at Hyatt Islandia Hotel, San Diego. Thurs-Sat. Contact: UCSD.

January 23-26—**Fracture Management.** UCD at Resort at Squaw Creek, Squaw Valley. Thurs-Sun. Contact: UCD.

PAIN MANAGEMENT

October 26—**Current Concepts in Pain: Diagnosis and Management.** Antelope Valley Hospital Medical Center at Antelope Valley Inn and Convention Center, Lancaster. Sat. 5 hrs. $60. Contact: Pamela Stones, (805) 949-5942.

November 15-16—**Pain Management.** UCD at Sterling Hotel, Napa. Fri-Sat. Contact: UCD.

December 11-15—**American Back Society Fall Symposium on Back Pain.** St. Francis Memorial Hospital Spine Center at Marriott, San Francisco. Wed-Sun. Contact: Aubrey Swartz, 2647 E 14th St, #401, Oakland 94601. (415) 536-9929.

February 19-22—**The Practicing Physician's Approach to the Difficult Headache Patient.** University of Chicago School of Medicine at Wyndham Hotel, Palm Springs. Wed-Sat. 15 hrs. Contact: Idell Applebaum, Diamond Headache Clinic, 5252 N Western Ave, Chicago, IL 60625. (312) 878-0396.

PATHOLOGY

November 8-9—**Advances in Rheumatology and Progress Against Infectious Diseases: Sixth Annual Kuzell Institute.** California Pacific Medical Center at Le Meridien Hotel, San Francisco. Fri-Sat. 12 hrs. $60. Contact: Continuing Education, (415) 923-3441.

January 10-11—**Pathology Update.** UCD at Cancer Center Auditorium. Fri-Sat. Contact: UCD.

PEDIATRICS

October 16-19—**16th Annual Pediatrics for the Practitioner.** Memorial/UCI Center for Health Education at Mauna Kea Beach Hotel, Kamuela, Hawaii. Wed-Sat. Contact: UCI.

November 20-23—**Pediatric Infectious Disease Seminar.** University of Toronto at Four Seasons Hotel, Newport Beach. Wed-Sat. Contact: University of Toronto, Medical Science Bldg, Toronto, Ontario M5S 1A8. (416) 978-2718.

January 22-25—**San Diego Conference on Responding to Child Maltreatment.** Children's Hospital at Hyatt Regency Hotel, La Jolla. Wed-Sat. Contact: Children's Hospital, 8001 Frost St, San Diego 92123. (619) 495-4940.

February 7-9—**Current Concepts in Pediatric Medicine: 1992.** Children's Hospital San Diego at Hyatt Islandia Hotel, San Diego. Fri-Sun. 18 hrs. Children's Hospital, (619) 576-4072.

March 4-6—**17th Annual Care of the Sick Newborn.** Memorial/UCI Center for Health Education at Long Beach. Wed-Fri. Contact: UCI.

PSYCHIATRY

November 8-10—**37th Annual Group Therapy Symposium.** UCSF at Handlery Union Square Hotel, San Francisco. Fri-Sun. 21 hrs. $210. Contact: UCSF.

January 26-31—**18th Annual Midwinter Program for Psychiatrists.** UCD at Hyatt Lake Tahoe. Sun-Fri. Contact: UCD.

RADIOLOGY

October 17-20—**1991 Annual Scientific Meeting.** Western Neuroradiological Society at Ritz Carlton Resort, Laguna Niguel. Thurs-Sun. Contact: Dawne Ryals, Ryals & Associates, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

October 20—**Magnetic Resonance Angiography.** UCSF at Hyatt Regency Hotel, San Francisco. Sun. 7 hrs. Contact: UCSF.

October 21-25—**Clinical Magnetic Resonance Imaging.** UCSF at Hyatt Regency Hotel, San Francisco. Mon-Fri. 32 hrs. $595. Contact: UCSF.

October 26-27—**Advanced Imaging of the Musculoskeletal System.** UCSD at Hotel del Coronado, San Diego. Sat-Sun. 9 hrs. $225. Contact: Dawne Ryals, Ryals & Associates, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

October 26-27—**Vascular Ultrasound: State of the Art.** UCSF at Ritz-Carlton Hotel, San Francisco. Sat-Sun. 12 hrs. $285. Contact: UCSF.

October 28-November 1—**Sixteenth Annual Postgraduate Radiology Course.** UCSD at Hotel del Coronado, San Diego. Mon-Fri. 28.25 hrs. $550. Contact: Dawne Ryals, Ryals & Associates, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

November 1-3—**11th Annual Interventional Radiology Course.** UCSD at Hotel del Coronado, San Diego. Fri-Sun. 15 hrs. $375. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

November 4-8—**Diagnostic Radiology Seminars.** UCSF at Hyatt Regency, Maui, Hawaii. Mon-Fri. 24 hrs. $595. Contact: UCSF.

November 15-17—**Advanced Seminars in Diagnostic Imaging.** UCSD at Ritz-Carlton Hotel, Laguna Niguel. Fri-Sun. $400. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

January 10-12—**Advanced Seminars in Diagnostic Imaging.** UCSD at Ritz-Carlton Resort Hotel, Laguna Niguel. Fri-Sun. 15 hrs. $400. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925 (404) 641-9773.

January 12-16—**Diagnostic Imaging Update: Body Imaging, Mammography, Neuroradiology and Pediatrics.** Stanford University Medical Center at Ritz-Carlton Palm Beach. Sun-Thurs. 23.5 hrs. $550. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

(Continued on Page 357)

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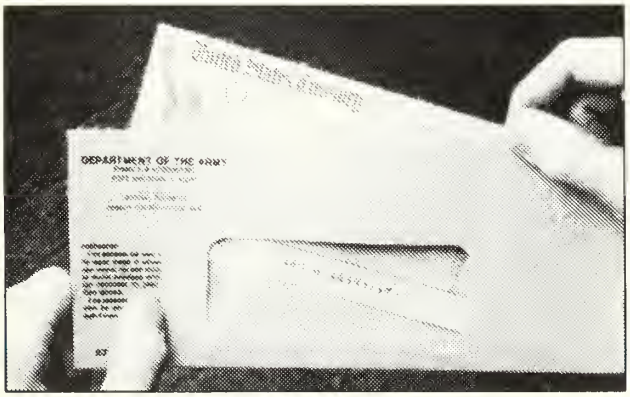

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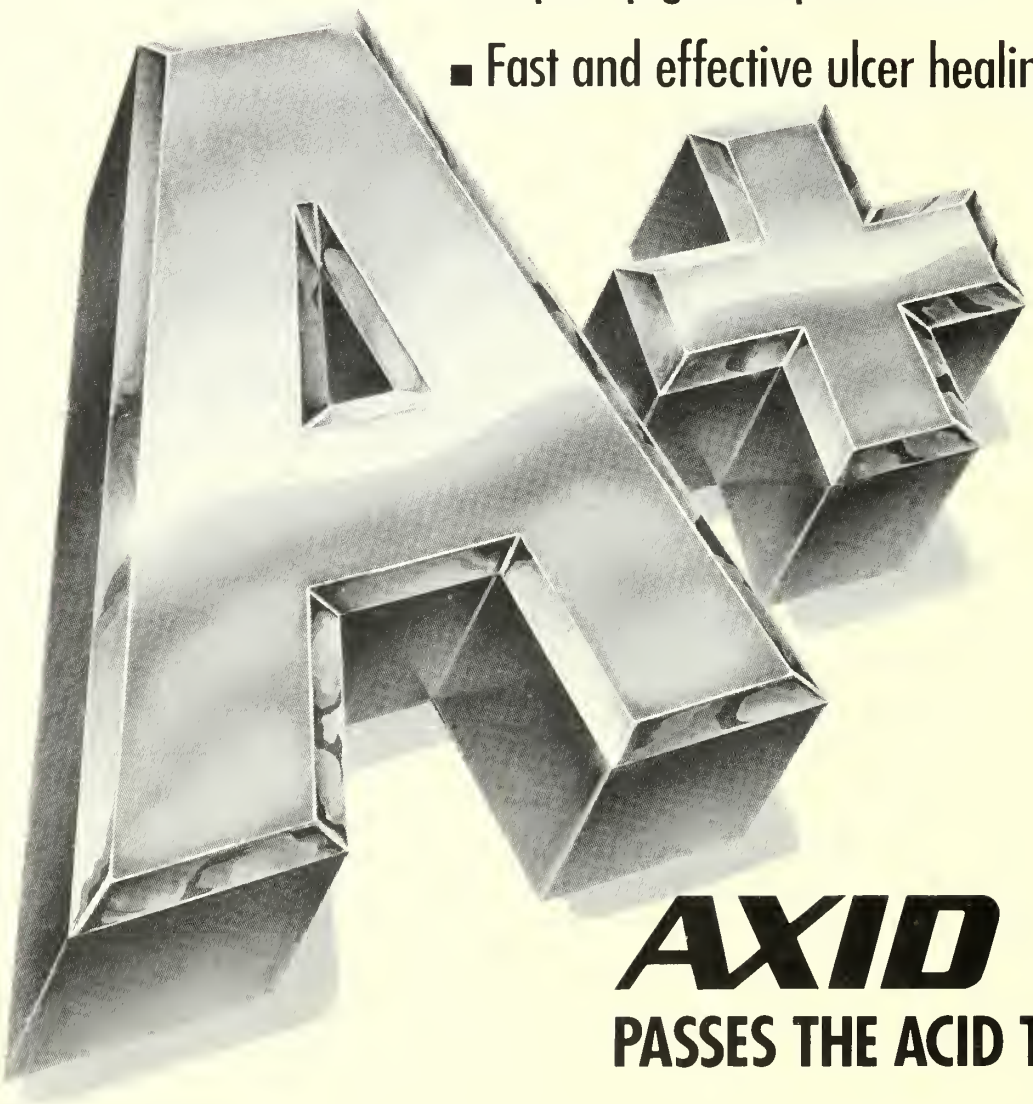

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See adjacent page for references and brief summary of prescribing information.

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Brief Summary. Consult the package insert for complete prescribing information.
Indications and Usage. 1. *Active duodenal ulcer*—for up to 8 weeks of treatment. Most patients heal within 4 weeks.
2. *Maintenance therapy*—for healed duodenal ulcer patients at a reduced dosage of 150 mg h.s. The consequences of therapy with Axid for longer than 1 year are not known.
Contraindications: Known hypersensitivity to the drug. Because cross sensitivity in this class of compounds has been observed, H_2-receptor antagonists, including Axid, should not be administered to patients with a history of hypersensitivity to other H_2-receptor antagonists.
Precautions: *General*—1. Symptomatic response to nizatidine therapy does not preclude the presence of gastric malignancy.
2. Dosage should be reduced in patients with moderate to severe renal insufficiency.
3. In patients with normal renal function and uncomplicated hepatic dysfunction, the disposition of nizatidine is similar to that in normal subjects.
Laboratory Tests—False-positive tests for urobilinogen with Multistix® may occur during therapy.
Drug Interactions—No interactions have been observed with theophylline, chlordiazepoxide, lorazepam, lidocaine, phenytoin, and warfarin. Axid does not inhibit the cytochrome P-450 enzyme system, therefore, drug interactions mediated by inhibition of hepatic metabolism are not expected to occur. In patients given very high doses (3,900 mg) of aspirin daily, increased serum salicylate levels were seen when nizatidine, 150 mg b.i.d., was administered concurrently.
Carcinogenesis, Mutagenesis, Impairment of Fertility—A 2-year oral carcinogenicity study in rats with doses as high as 500 mg/kg/day (about 80 times the recommended daily therapeutic dose) showed no evidence of a carcinogenic effect. There was a dose-related increase in the density of enterochromaffin-like (ECL) cells in the gastric oxyntic mucosa. In a 2-year study in mice, there was no evidence of a carcinogenic effect in male mice, although hyperplastic nodules of the liver were increased in the high-dose males as compared with placebo. Female mice given the high dose of Axid (2,000 mg/kg/day, about 330 times the human dose) showed marginally statistically significant increases in hepatic carcinoma and hepatic nodular hyperplasia with no numerical increase seen in any of the other dose groups. The rate of hepatic carcinoma in the high-dose animals was within the historical control limits seen for the strain of mice used. The female mice were given a dose larger than the maximum tolerated dose, as indicated by excessive (30%) weight decrement as compared with concurrent controls and evidence of mild liver injury (transaminase elevations). The occurrence of a marginal finding at high dose only in animals given an excessive and somewhat hepatotoxic dose, with no evidence of a carcinogenic effect in rats, male mice, and female mice (given up to 360 mg/kg/day, about 60 times the human dose), and a negative mutagenicity battery are not considered evidence of a carcinogenic potential for Axid.
Axid was not mutagenic in a battery of tests performed to evaluate its potential genetic toxicity, including bacterial mutation tests, unscheduled DNA synthesis, sister chromatid exchange, mouse lymphoma assay, chromosome aberration tests, and a micronucleus test.
In a 2-generation, perinatal and postnatal fertility study in rats, doses of nizatidine up to 650 mg/kg/day produced no adverse effects on the reproductive performance of parental animals or their progeny.
Pregnancy—Teratogenic Effects—Pregnancy Category C—Oral reproduction studies in rats at doses up to 300 times the human dose and in Dutch Belted rabbits at doses up to 55 times the human dose revealed no evidence of impaired fertility or teratogenic effect; but, at a dose equivalent to 300 times the human dose, treated rabbits had abortions, decreased number of live fetuses, and depressed fetal weights. On intravenous administration to pregnant New Zealand White rabbits, nizatidine at 20 mg/kg produced cardiac enlargement, coarctation of the aortic arch, and cutaneous edema in 1 fetus, and at 50 mg/kg, it produced ventricular anomaly, distended abdomen, spina bifida, hydrocephaly, and enlarged heart in 1 fetus. There are, however, no adequate and well-controlled studies in pregnant women. It is also not known whether nizatidine can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Nizatidine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
Nursing Mothers—Studies in lactating women have shown that 0.1% of an oral dose is secreted in human milk in proportion to plasma concentrations. Because of growth depression in pups reared by treated lactating rats, a decision should be made whether to discontinue nursing or the drug, taking into account the importance of the drug to the mother.
Pediatric Use—Safety and effectiveness in children have not been established.
Use in Elderly Patients—Healing rates in elderly patients were similar to those in younger age groups as were the rates of adverse events and laboratory test abnormalities. Age alone may not be an important factor in the disposition of nizatidine. Elderly patients may have reduced renal function.
Adverse Reactions: Clinical trials of varying durations included almost 5,000 patients. Among the more common adverse events in domestic placebo-controlled trials of over 1,900 nizatidine patients and over 1,300 on placebo, sweating (1% vs 0.2%), urticaria (0.5% vs <0.01%), and somnolence (2.4% vs 1.3%) were significantly more common with nizatidine. It was not possible to determine whether a variety of less common events were due to the drug.
Hepatic—Hepatocellular injury (elevated liver enzyme tests or alkaline phosphatase) possibly or probably related to nizatidine occurred in some patients. In some cases, there was marked elevation (>500 IU/L) in SGOT or SGPT and, in a single instance, SGPT was >2,000 IU/L. The incidence of elevated liver enzymes overall and elevations of up to 3 times the upper limit of normal, however, did not significantly differ from that in placebo patients. All abnormalities were reversible after discontinuation of Axid. Since market introduction, hepatitis and jaundice have been reported. Rare cases of cholestatic or mixed hepatocellular and cholestatic injury with jaundice have been reported with reversal of the abnormalities after discontinuation of Axid.
Cardiovascular—In clinical pharmacology studies, short episodes of asymptomatic ventricular tachycardia occurred in 2 individuals administered Axid and in 3 untreated subjects.
CNS—Rare cases of reversible mental confusion have been reported.
Endocrine—Clinical pharmacology studies and controlled clinical trials showed no evidence of antiandrogenic activity due to nizatidine. Impotence and decreased libido were reported with equal frequency by patients on nizatidine and those on placebo. Gynecomastia has been reported rarely.
Hematologic—Fatal thrombocytopenia was reported in a patient treated with nizatidine and another H_2-receptor antagonist. This patient had previously experienced thrombocytopenia while taking other drugs. Rare cases of thrombocytopenic purpura have been reported.
Integumental—Sweating and urticaria were reported significantly more frequently in nizatidine- than in placebo-treated patients. Rash and exfoliative dermatitis were also reported.
Hypersensitivity—As with other H_2-receptor antagonists, rare cases of anaphylaxis following nizatidine administration have been reported. Rare episodes of hypersensitivity reactions (eg, bronchospasm, laryngeal edema, rash, and eosinophilia) have been reported.
Other—Hyperuricemia unassociated with gout or nephrolithiasis was reported. Eosinophilia, fever, and nausea related to nizatidine have been reported.
Overdosage: Overdoses of Axid have been reported rarely. If overdosage occurs, activated charcoal, emesis, or lavage should be considered along with clinical monitoring and supportive therapy. Renal dialysis does not substantially increase clearance of nizatidine due to its large volume of distribution.

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References
1. Data on file, Lilly Research Laboratories
2. *Scand J Gastroenterol* 1987,22(suppl 136):61-70.
3. *Scand J Gastroenterol* 1987,22(suppl 136):47-55
4. *Am J Gastroenterol* 1989,84:769-774

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CONTINUING MEDICAL EDUCATION

(Continued from Page 354)

January 31-February 2—**44th Annual Midwinter Radiological Conference.** Los Angeles Radiological Society at Century Plaza Hotel, Los Angeles. Fri-Sun. 17.25 hrs. $425. Contact: LARS, PO Box 91215, Los Angeles 90009-1215. (213) 827-9078.

February 4-7—**Advanced Seminars in Diagnostic Imaging.** UCSD at Le Meridien Hotel, Coronado. Tues-Fri. 20 hrs. $500. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

February 4-8—**18th Annual Mid-Pacific Radiological Conference.** Los Angeles Radiological Society at Hyatt Regency Waikoloa, Hawaii. Tues-Sat. 18.5 hrs. $550. Contact: LARS, PO Box 91215, Los Angeles 90009-1215. (213) 827-9078.

February 10-13—**Mammographically Detected Early Breast Cancer.** University of Alabama at Birmingham at Ritz-Carlton, Rancho Mirage. Mon-Thurs. 18 hrs. $450. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

February 24-28—**Diagnostic Imaging Update: Body Imaging, Mammography, MRI and Interventional.** Stanford University Medical Center at Ritz-Carlton Mauna Lani, Hawaii. Mon-Fri. 23.5 hrs. $550. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

February 27-March 1—**Advanced Seminars in Diagnostic Imaging.** UCSD at Ritz-Carlton, Laguna Niguel. Thurs-Sun. 20 hrs. $500. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

March 2-6—**Magnetic Resonance Imaging.** UCSD at Hotel del Coronado, San Diego. Mon-Fri. 27.25 hrs. $540. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

REHABILITATIVE/THERAPEUTIC

November 14-16—**3rd Triennial Symposium on New Directions in Antiviral Chemotherapy.** UCSF at Sheraton Palace Hotel, San Francisco. Thurs-Sat. 19 hrs. $200. Contact: UCSF.

SURGERY

October 27-30—**Preparing for Surgery: Medical Evaluation of the Preoperative Patient.** American College of Physicians and UCD at La Playa Hotel, Carmel. Sun-Wed. Contact: ACP, Independence Mall West, 6th St at Race, Philadelphia, PA 19106-1572. (800) 523-1546, ext. 2429.

November 2-9—**13th International Seminar on Operative Arthroscopy.** UCLA at Ritz-Carlton, Mauna Lani Resort, Hawaii. 1 week. 37 hrs. $995. Contact: UCLA.

December 5-6—**Advanced Techniques in Laparoscopic Surgery.** UCD. Thurs-Fri. 15 hrs. $3200. Contact: UCD.

January 17-18—**What's New in General Surgery.** UCD at Radisson Hotel, Sacramento. Fri-Sat. 16 hrs. $295. Contact: UCD.

February 8-11—**International Symposium on Hair Replacement Surgery.** American Academy of Facial Plastic and Reconstructive Surgery at Century City J W Marriott, Los Angeles. Sat-Tues. Contact: Sharon Clawson, (213) 278-8823.

March 19-22—**42nd Annual Surgical Forum.** Society of Graduate Surgeons at Beverly Hilton, Beverly Hills. Thurs-Sun. Contact: SGS, 5820 Wilshire Blvd, Ste 500, Los Angeles 90036. (213) 937-5514.

GENERAL/MULTIDISCIPLINARY

October 24-26—**Medicine Today.** UCSD at Price Center. Sat-Sun. Contact: UCSD.

November 10—**Management of Cranial Base Disease.** UCSF Multidisciplinary Panel on Skull Base Diseases at Ritz Carlton Hotel, San Francisco. Sun. 8 hrs. $100. Contact: UCSF.

December 9-10—**Clinical Care of the AIDS Patient.** UCSF at San Francisco Marriott Hotel. Mon-Tues. 13 hrs. $250. Contact: UCSF.

March 12-13—**Dimensions of Caring 1992: Enhancing Quality of Life in Palliative Care.** Scripps Clinic and Research Foundation at Omni Hotel, San Diego. Thurs-Fri. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

COLORADO

This listing of continuing medical education programs in Colorado is compiled by the Denver Medical Society. To list CME programs here, please send information at least two months in advance to: Mr Robert L. Kennedy, Denver Medical Society, 1850 Williams Street, Denver, CO 80218; or telephone (303) 377-1850.

Brochures, course information, and registration forms are available from the contact person or organization.

(Continued on Page 358)

(Continued from Page 357)

October 25-26—**14th Annual Perinatal Conference.** Children's Hospital of Denver at Laramie, Wyoming. Fri-Sat. Contact: Christine Sievers-Spencer, (303) 861-6413.

November 7-10—**Rural Perinatal Traineeship Program.** Children's Hospital, Denver. Thurs-Sun. Contact: Christine Sievers-Spencer, (303) 861-6413.

November 14—**Pre-term Infant Feeding Conference.** University of Colorado Health Sciences Center, Denver. Thurs. Contact: Trish Beachy or Nancy Briggs, (303) 270-7117.

November 22-23—**Colorado Springs Perinatal Conference.** Children's Hospital of Denver at Colorado Springs. Fri-Sat. Contact: Christine Sievers-Spencer, (303) 861-6413.

December 2-6—**Respiratory Therapy Traineeship Program.** Children's Hospital, Denver. Mon-Fri. Contact: Jeff Griebel, (303) 861-6188.

January 25-February 1—**15th Annual Infectious Diseases in Clinical Practice.** UCSF at Beaver Run Resort and Conference Center, Breckenridge. Sat-Sat. 24 hrs. Contact: UCSF.

First Wednesday of Each Month—**Various Topics in Neurology.** Sponsored by the Colorado Society of Clinical Neurologists. Contact: Colorado Society of Neurologists, (303) 449-3566.

CONTACT INFORMATION

U of Colo—Contact: University of Colorado School of Medicine, Office of Continuing Medical Education, 4200 E 9th Ave, Denver, CO. (303) 270-5195.

NEW MEXICO

Information, requests for accreditation, and items to be listed should be sent to the chair of the CME Committee, New Mexico Medical Society, 7770 Jefferson, Suite 400, Albuquerque, NM 87109, at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 828-0237.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

November 1-3—**The 12 Lead ECG for the Primary Care Physician.** Presbyterian Hospital, Albuquerque. Contact: Jan Grieve, New Mexico Heart Clinic, 1001 Coal SE, Albuquerque 87106. (505) 242-2796 or (800) 888-6642.

November 8—**G.I. Update 1991.** Marriott Hotel, Albuquerque. Contact: Ann Winter, St Joseph Health Care Systems, 601 Grand NE, Albuquerque 87102. (505) 246-8004.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. Accredited institutions wishing to list AMA Category 1 CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, UT 84102; or phone (801) 355-5290. For information on CME accreditation, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution.

MEDICAL GRAND ROUNDS

Each Wed—8:00-9:00 a.m. Alternating between University of Utah Medical Center and VA Medical Center, Salt Lake City. Contact: William D. Odell, MD, PhD, Professor and Chairman, Dept of Internal Medicine, Univ of Utah, (801) 581-7606.

* * *

November 15-16—**Laser Surgery—Laparoscopic Cholesystectomy** (Sponsor: UUSM). Fri-Sat. The Laser Institute, University of Utah, Salt Lake City. Contact: (801) 581-7001.

SPONSORS OF COURSES—ABBREVIATIONS

AHA:	American Heart Association, Utah Affiliate, 645 E 400 South, Salt Lake City 84102. (801) 322-5601.
CH:	Castleview Hospital (formerly Carbon Hospital), RFD 2, Box 46, Price 84501. (801) 637-4800.
HCH:	Holy Cross Hospital, 1045 E First South, Salt Lake City 84102. (801) 350-4744.
ITS:	Intermountain Thoracic Society, 1616 S 11th East, Salt Lake City 84105. (801) 484-4456.
LDSH:	LDS Hospital, 8th Ave and "C" St, Salt Lake City 84143. (801) 321-1100.
LRH:	Logan Regional Hospital, 1400 N 5th East, Logan 84321. (801) 752-2050.
MDH:	McKay-Dee Hospital Center, 3939 Harrison Blvd, Ogden 84409. (801) 399-4141.
MVH:	Mountain View Hospital, 1000 E Highway 6, Payson 84651. (801) 465-9201.
144:	144th Evacuation Hospital, PO Box 8000, Salt Lake City 84108. (801) 524-3924.
OSS:	Ogden Surgical Society, PO Box 9311, Ogden 84409.
PVH:	Pioneer Valley Hospital, 3460 S 4155 West, West Valley City 84120. (801) 968-9061.
UOS:	Utah Ophthalmological Society, 540 E 500 South, Salt Lake City 84102. (801) 355-7477.
USH:	Utah State Hospital, PO Box 270, Provo 84603-0270. (801) 373-4400.
UUSM:	University of Utah School of Medicine, Office of Continuing Medical Education, 50 N Medical Dr, Salt Lake City 84132. (801) 581-8664.
VAMC:	Veterans Administration Medical Center, 500 Foothill Dr, Salt Lake City 84148. (801) 582-1565.
VVMC:	Valley View Medical Center, 595 S 75 East, Cedar City 84720. (801) 586-6587.
WRI:	Western Rehabilitation Institute, 8074 S 1300 East, Sandy 84094. (801) 561-3400.

WASHINGTON

The listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here, please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle, WA 98121; or phone (206) 441-WSMA.

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

October 17-19—**Endoscopic Sinus Surgery.** Seattle. Thurs-Sat. Contact: U/W.

October 18—**Atypical Pneumonia Syndromes.** Seattle. Fri. Contact: VMMC.

October 18-20—**Spinal Cord Injury.** Seattle. Fri-Sun. Contact: U/W.

October 24—**Geriatrics.** Everett. Thurs. Contact: Pacific Northwest Medical Education Institute, (206) 258-6322.

November 1—**Radiosurgery Update.** Seattle. Fri. Contact: VMMC.

(Continued on Page 359)

CONTINUING MEDICAL EDUCATION

(Continued from Page 358)

November 7-8—**Drug Update: Prescription for the '90s.** Seattle. Thurs-Fri. Contact: (206) 258-6322.

November 8—**25th Annual Cancer Conference.** Seattle. Fri. Contact: VMMC.

November 14-15—**Drug Therapy.** Seattle. Thurs-Fri. Contact: U/W.

December 6—**Practical Pediatrics.** Seattle. Fri. Contact: VMMC.

December 6-7—**Urology.** Seattle. Fri-Sat. Contact: (206) 441-9762.

December 12-14—**American College of Physicians.** Seattle. Thurs-Sat. Contact: U/W.

December 12-14—**7th Annual ID Conference.** Everett. Thurs-Sat. Contact: Pacific Northwest Medical Education Institute, (206) 258-6322.

COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Avenue, Seattle, WA 98104 (206) 223-5953.

PCMS CME—Contact: Mrs Maxine Bailey, Executive Director, College of Medical Education, 705 South Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON)—Contact. U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

WSMA—Washington State Medical Association, Continuing Medical Education, 2033 Sixth Ave, Suite 900, Seattle, WA 98121. (206) 441-9762.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, PO Box 900, Seattle, WA 98111. (206) 223-6898.

WYOMING

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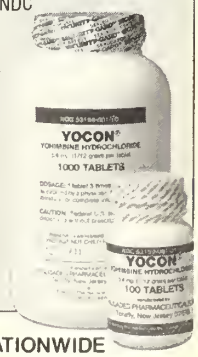

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1. A. Morales et al., New England Journal of Medicine: 1221. November 12, 1981.
2. Goodman, Gilman — The Pharmacological basis of Therapeutics 6th ed., p. 176-188. McMillan December Rev. 1/85.
3. Weekly Urological Clinical letter, 27:2, July 4, 1983.
4. A. Morales et al., The Journal of Urology 128: 45-47, 1982.

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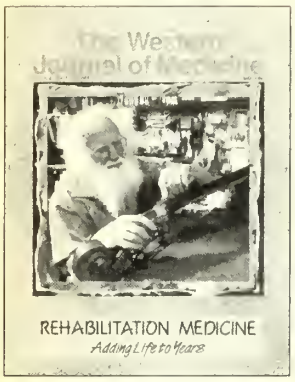

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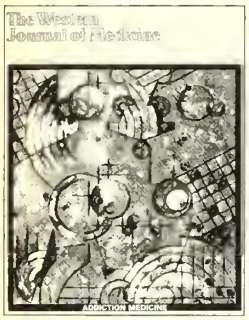

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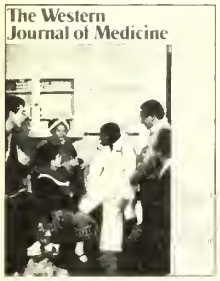

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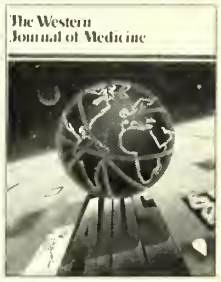

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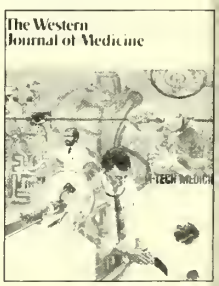

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2. Berman SM, Shah B, Wyle FA, Dacosta-Iyer M, McRae DM: Disseminated *Pneumocystis carinii* in a patient receiving aerosolized pentamidine prophylaxis. West J Med 1990; 153:82-86

Books

3. Berne EJ: Role playing in therapy, chap 2, Principles of Group Therapy. New York, NY, Oxford University Press, 1966, pp 35-51 (author of book is same as author of chapter)

4. Munsung JD: The role of drugs, chap 2, *In* Brest AN, Mayer JD (Eds): Hypertension—Vol 3, Therapy, 2nd Ed. Chicago, Ill, Year Book Medical Publishers, 1961, pp 456-479 (authors of book differ from chapter author)

Correspondence

5. Shusterman D: Espresso maker's wrist (Correspondence). West J Med 1990; 152:721-722

Government Publications

6. The Health Consequences of Smoking—Cardiovascular Disease: A Report of the Surgeon General. Washington, DC, US Dept of Health and Human Services publication No. (PHS) 84-50204, 1983

7. Centers for Disease Control: Update: Acquired immunodeficiency syndrome—United States. MMWR 1987; 36:522-526

Proceedings

8. O'Connell M: A Controlled Trial of Regional Intra-arterial FUDR Versus Systemic 5FU for the Treatment of Metastatic Colorectal Cancer Confined to the Liver. Presented at the annual meeting of the American Society of Clinical Oncology, San Francisco, December 1989

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(T. Harris, "Selenium-Rich Sediments Also Have Been Reported in Wildlife Refuges," *The Sacramento Bee*, September 8, 1985, p 5)

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Lyme disease has been reported in red squirrels (J. Sneed, PhD, Department of Wildlife, written communication, September 1990).

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Contraindications: *Tagamet is contraindicated for patients known to have hypersensitivity to the product*

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Tagamet has been reported to reduce the hepatic metabolism of warfarin-type anticoagulants, phenytoin, propranolol, chlordiazepoxide, diazepam, certain tricyclic antidepressants, lidocaine, theophylline and metronidazole Clinically significant effects have been reported with the warfarin anticoagulants, therefore, close monitoring of prothrombin time is recommended, and adjustment of the anticoagulant dose may be necessary when Tagamet is administered concomitantly Interaction with phenytoin, lidocaine and theophylline has also been reported to produce adverse clinical effects

However, a crossover study in healthy subjects receiving either Tagamet 300 mg q i d or 800 mg h s concomitantly with a 300 mg b i d dosage of theophylline (Theo-Dur®, Key Pharmaceuticals, Inc) demonstrated less alteration in steady-state theophylline peak serum levels with the 800 mg h s regimen, particularly in subjects aged 54 years and older Data beyond ten days are not available (Note All patients receiving theophylline should be monitored appropriately, regardless of concomitant drug therapy)

In a 24-month toxicity study in rats, at dose levels approximately 8 to 48 times the recommended human dose, benign Leydig cell tumors were seen These were common in both the treated and control groups, and the incidence became significantly higher only in the aged rats receiving Tagamet

A weak antiandrogenic effect has been demonstrated in animals In human studies, Tagamet has been shown to have no effect on spermatogenesis, sperm count, motility, morphology or in vitro fertilizing capacity

Pregnancy Category B Reproduction studies have been performed in rats, rabbits and mice at doses up to 40 times the normal human dose and have revealed no evidence of impaired fertility or harm to the fetus due to Tagamet There are, however, no adequate and well-controlled studies in pregnant women Because animal reproductive studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed

Lack of experience to date precludes recommending Tagamet for use in children under 16 unless anticipated benefits outweigh potential risks, generally, nursing should not be undertaken by patients taking the drug since cimetidine is secreted in human milk

Adverse Reactions: *Diarrhea, dizziness, somnolence, headache Reversible confusional states (e g , mental confusion, agitation, psychosis, depression, anxiety, hallucinations, disorientation), predominantly in severely ill patients, have been reported Reversible impotence in patients with pathological hypersecretory disorders receiving Tagamet, particularly in high doses for at least 12 months, has been reported The incidence of impotence in large-scale surveillance studies at regular doses has not exceeded that commonly reported in the general population Gynecomastia has been reported in patients treated for one month or longer Decreased white blood cell counts in Tagamet-treated patients (approximately 1 per 100,000 patients), including agranulocytosis (approximately 3 per million patients), have been reported, including a few reports of recurrence on rechallenge Most of these reports were in patients who had serious concomitant illnesses and received drugs and/or treatment known to produce neutropenia Thrombocytopenia (approximately 3 per million patients) and, very rarely, cases of aplastic anemia have also been reported Dose-related increases in serum transaminase have been reported Reversible adverse hepatic effects, cholestatic or mixed cholestatic-hepatocellular in nature, have been reported rarely Because of the predominance of cholestatic features, severe parenchymal injury is considered highly unlikely A single case of biopsy-proven periportal hepatic fibrosis in a patient receiving Tagamet has been reported Small, possibly dose-related increases in plasma creatinine have been reported Rare cases of fever, interstitial nephritis, urinary retention, pancreatitis and allergic reactions, including anaphylaxis and hypersensitivity vasculitis, have been reported Rare cases of bradycardia, tachycardia and A-V heart block have been reported with H_2-receptor antagonists Reversible arthralgia, myalgia and exacerbation of joint symptoms in patients with preexisting arthritis have been reported rarely Rare cases of polymyositis have been reported, but no causal relationship has been established Mild rash and, very rarely, cases of severe generalized skin reactions (e g , Stevens-Johnson syndrome, epidermal necrolysis, erythema multiforme, exfoliative dermatitis and generalized exfoliative erythroderma) have been reported with H_2-receptor antagonists Reversible alopecia has been reported very rarely*

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Biomedical Science

Mechanisms and Consequences of Leukocyte-Endothelial Interaction

JOHN M. HARLAN, MD, NICHOLAS B. VEDDER, MD, ROBERT K. WINN, PhD, *and* CHARLES L. RICE, MD, *Seattle, Washington*

Presented at the annual meeting of the Western Association of Physicians, Carmel, California, February 6-7, 1991.

Leukocyte adhesion to endothelium is a critical event in host defense against microorganisms and in the repair of tissue damage. Under some circumstances, however, altered leukocyte-endothelial interactions may contribute to the pathogenesis of inflammatory and immune diseases. In a number of experimental models, the inhibition of leukocyte adherence to endothelium substantially reduces vascular and tissue injury. Antiadhesion therapy may represent a novel approach to the treatment of a wide spectrum of clinical disorders.

(Harlan JM, Vedder NB, Winn RK, Rice CL: Mechanisms and consequences of leukocyte-endothelial interaction. West J Med 1991 Oct; 155:365-369)

A new approach to the treatment of inflammatory and immune disorders has recently emerged from clinical observations, cell and molecular biology studies, and investigations in animal models of disease. The focus of this approach is the interaction of circulating leukocytes with vascular endothelium.[1] In response to diverse extravascular stimuli such as infection, foreign antigen, or tissue damage, signals are generated that activate either the leukocyte or the endothelial cell. As a consequence of activation, one or both cell types become adhesive for the other, leading to increased leukocyte adherence to endothelium at the site of inflammation or immune reaction. The adherent leukocyte then moves across the vessel wall to extravascular sites, diapedesing between endothelial cells and migrating through the subendothelial matrix to tissue. There it participates in inflammatory or immune reactions. Because the leukocyte must adhere to the endothelium to emigrate to the extravascular site, considerable attention has been focused on the leukocyte and endothelial cell surface molecules that mediate this adhesive interaction.

In the past ten years, more than a dozen proteins involved in the adherence of leukocytes to endothelium have been functionally and immunochemically identified and molecularly cloned.[2,3] Leukocyte-endothelial adhesion molecules can be divided into two categories: integrin receptors on leukocytes that interact with ligands on the endothelial cell and that are members of the immunoglobulin gene superfamily, and a new class of proteins, LEC-CAMs or "selectins," that recognize specific carbohydrate counterstructures on the endothelial cell or on the leukocyte. In this brief review we will focus on the leukocyte integrin receptor that mediates neutrophil adherence to endothelium.

As with many other problems in biology, important insights into the molecular basis of leukocyte adherence to endothelium have come from studies of a genetic deficiency syndrome. Leukocyte adhesion deficiency or leukocyte-cell adhesion molecule-deficiency syndrome results from a partial or complete deficiency of the leukocyte adhesion receptor complex, CD11/CD18 (CD refers to cluster differentiation).[4-6] The CD11/CD18 complex consists of three heterodimeric subunits. Each subunit contains a common β-chain, designated CD18, and a distinct α-chain, designated CD11a, CD11b, or CD11c. The heterodimeric subunits are also commonly known as LFA-1 (CD11a/CD18); Mac-1 or Mo1 (CD11b/CD18), which is also the complement receptor type 3 (CR3); and p150,95 (CD11c/CD18). LFA-1 is found on all leukocytes, whereas Mac-1 and p150,95 are restricted to phagocytes and natural killer cells (Figure 1). The three α-chains and the common β-chain have been molecularly cloned by a number of groups and shown to be members of the integrin superfamily of adhesion receptors (reviewed by Arnaout and Larson and Springer[6,7]). The CD11/CD18 complex makes up the β_2 subclass of this family and is found only on leukocytes.

The CD11/CD18-deficiency syndrome is inherited in an autosomal recessive manner; heterozygotes have no signifi-

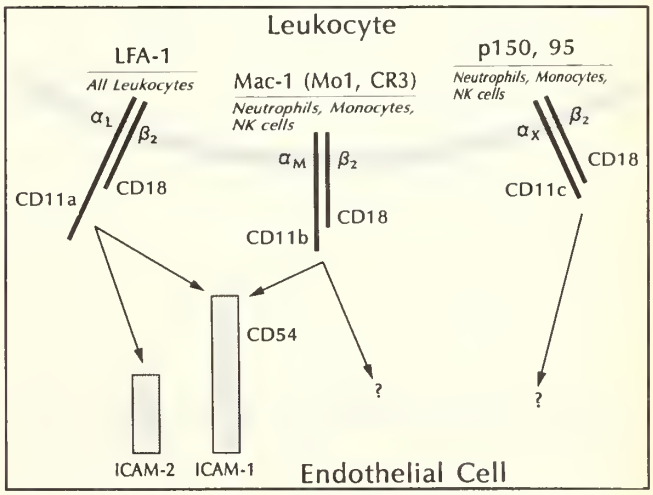

Figure 1.—The leukocyte CD11/CD18 complex and its endothelial ligands, intercellular adhesion molecules-1 and -2 (ICAM-1, ICAM-2), are shown. NK = natural killer

From the Department of Medicine, Division of Hematology (Dr Harlan), and the Department of Surgery (Drs Vedder, Winn, and Rice), University of Washington School of Medicine, Seattle.

Dr Harlan receives research funding in the field of cell adhesion from Cytel Corporation, La Jolla, California.

Reprint requests to John M. Harlan, MD, Division of Hematology RM-10, University of Washington, Seattle, WA 98195.

cant clinical manifestations. The molecular basis of the CD11/CD18-deficiency syndrome has been shown to result from heterogeneous mutations in the common β-chain.[8] A complete failure to synthesize any β-chain or the synthesis of only abnormal β-chain does not allow association of the three α-chains with the β-chain in heterodimers and thereby prevents their insertion into the plasma membrane. Such persons have a complete absence of surface membrane CD11/CD18 and exhibit a severe phenotype. Persons with mutations allowing the synthesis of some functional β-chain have a partial deficiency and mild to moderate phenotype. Interestingly, the CD11/CD18-deficiency syndrome has been reported as a granulocytopathy syndrome in a dog and in Holstein cows.[9,10]

The clinical manifestations of the CD11/CD18-deficiency syndrome have been reviewed in detail.[4-6] The CD11/CD18-deficient patients frequently present with delayed separation of the umbilical cord at birth, presumably resulting from impaired wound healing. Severely affected patients suffer from recurrent, sometimes life-threatening bacterial infections throughout life. The infections often begin at skin or mucous membranes and may progress to overt sepsis. The most striking feature of CD11/CD18 deficiency is the absence of neutrophils and monocytes at the sites of infection—that is, the patients have a failure to suppurate. Despite this profound defect in phagocyte migration, CD11/CD18-deficient patients have chronic neutrophilic leukocytosis with leukocyte counts as high as 100×10^9 per liter (100,000 per μl) during episodes of acute infection. Presumably, the signals required to mobilize neutrophils from stores in the bone marrow, such as colony-stimulating factors, are intact, and the CD11/CD18-deficient cells accumulate in the circulation because of their inability to migrate.

All of the major clinical manifestations of CD11/CD18-deficiency syndrome can be ascribed to the defect in phagocyte migration. This defect is most dramatically evidenced by the absence of pus at the sites of infection. Also, the patients' neutrophils fail to migrate normally to skin chambers or skin windows. Transfused allogenic neutrophils do migrate to skin windows or extravascular sites of infection,[11] and granulocyte transfusions have been used successfully in some patients with refractory infections. This response to allogeneic leukocyte transfusions indicates that all of the other humoral and cellular mechanisms required for leukocyte emigration are intact in CD11/CD18-deficient patients and that the defect is intrinsic to the leukocyte.

A number of severely affected patients with CD11/CD18 deficiency have been successfully treated by allogeneic bone marrow transplantation.[12] Because the syndrome results from a single gene defect in hematopoietic cells, it is an attractive candidate disease for gene therapy.[13,14]

The profound defect in phagocyte emigration in this syndrome results from an inability of the CD11/CD18-deficient phagocytes to adhere to endothelial cells at sites of inflammation or infection. The abnormality in phagocyte adherence to endothelium was first demonstrated in vitro using purified neutrophils isolated from an affected patient and endothelial cells from cultured human umbilical vein.[15] Normal neutrophils have a low basal adherence to cultured endothelium but can be stimulated to increase binding markedly with various activating agents such as bacterial chemotactic peptide, platelet-activating factor, tumor necrosis factor, interleukin-8, or complement fragment C5a. CD11/CD18-deficient neutrophils fail to augment adherence when stimulated, and this defect in stimulated adherence is reproduced in normal neutrophils by monoclonal antibodies directed at functional epitopes on the α (CD11b)- or β (CD18)-chains of the Mac-1 subunit and to a lesser extent with monoclonal antibodies to α-chain (CD11a) of the LFA-1 subunit. The inability of CD11/CD18-deficient neutrophils to adhere to endothelium when stimulated also results in an inability to migrate across the endothelial monolayer in response to chemotactic stimuli.[15]

The CD11/CD18 complex is involved not only in the heterotypic adhesion of neutrophils to other cells such as endothelial cells but also in the homotypic adhesion or aggregation of neutrophils. When neutrophils have exposure to a wide variety of stimuli, they rapidly form homotypic aggregates. This aggregation response is completely absent in CD11/CD18-deficient neutrophils and is abolished in normal neutrophils by monoclonal antibodies to CD11b or CD18.[16]

The availability of blocking monoclonal antibodies that cross-react with CD11b or CD18 in other species has allowed an investigation of the role of the CD11/CD18 complex in the in vivo interaction of neutrophils and endothelium. Administering CD11b or CD18 monoclonal antibodies has been shown to inhibit neutrophil migration to experimentally induced sites of inflammation in the skin, peritoneum, lungs, joints, and meninges.[2] The CD11b or CD18 monoclonal antibodies do not reduce the circulating neutrophil count but, in fact, produce leukocytosis similar to that observed in patients with CD11/CD18 deficiency. Studies using intravital microscopy have confirmed that the blockade in neutrophil migration produced by these CD11b or CD18 monoclonal antibodies is due to inhibited adherence of leukocytes to endothelium. Superfusion of the microcirculation with a chemoattractant produces leukocyte adherence to vessel walls, intravascular aggregation of leukocytes, and leukocyte diapedesis across vessel walls to extravascular tissue. Pretreatment with a CD18 monoclonal antibody completely abolishes aggregation and sticking.[17] Of interest, although the CD18 monoclonal antibody prevented "sticking," the leukocytes continued to "roll" along the vessel wall. The rolling of leukocytes along the vessel thus appears to be mediated by adhesion molecules other than the CD11/CD18 complex.

Two of the endothelial counterstructures for the CD11/CD18 complex have been identified as intercellular adhesion molecules 1 and 2 (ICAM-1, CD54; ICAM-2) (Figure 1).[18,19] ICAM-1 and ICAM-2 are both members of the immunoglobulin superfamily of proteins that interact with the LFA-1 subunit (CD11a/CD18).[20] ICAM-1 also binds the Mac-1 subunit (CD11b/CD18).[20] There appear to be other counterstructures for Mac-1 and p150,95 (CD11c/CD18) on endothelium that have not yet been identified.

In pronounced contrast to neutrophils, lymphocyte traffic in CD11/CD18-deficient patients appears to be normal, although their lymphocytes also lack CD11/CD18. Biopsy specimens of tissue at sites of inflammation or immune reaction show an infiltration of lymphocytes, occasional eosinophils, and rare monocytes but no neutrophils.[4,11] Moreover, cell-mediated immune responses are largely intact as the patients show delayed-type hypersensitivity reactions and do not usually suffer from viral or opportunistic infections. Obviously, lymphocytes, monocytes, eosinophils, and other

cell types must possess an adhesion receptor(s) other than CD11/CD18 that is capable of mediating binding to endothelium. Selectin molecules may play an important role in this CD11/CD18-independent mechanism of binding. The β_1 integrin receptor, very-late-activation antigen-4 (VLA-4; CD49d/CD29), however, is the most likely candidate for this alternate pathway of adhesion and emigration. VLA-4 binds to vascular cell adhesion molecule-1 (VCAM-1), a cytokine-induced endothelial protein that is a member of the immunoglobulin superfamily.[21-23] Most important, VLA-4 is expressed on all leukocyte classes except neutrophils. Thus, the CD11/CD18-deficiency syndrome with its profound defect in neutrophil adhesion and migration likely occurs because neutrophils uniquely lack this alternate integrin receptor.

It is clear from clinical manifestations of CD11/CD18 deficiency that neutrophil adherence to endothelium is a critical event in host defense. Under some circumstances, however, neutrophil adhesion to endothelium may have deleterious consequences for the host. Exaggerated or unregulated neutrophil adhesion may lead to endothelial damage by toxic products, such as proteases and oxidants, released by the adherent neutrophil. Altered neutrophil-endothelial interactions have been implicated in the pathogenesis of vascular and tissue injury in a wide variety of clinical disorders including sepsis, inflammatory skin diseases, the adult respiratory distress syndrome, vasculitides, and some forms of glomerulonephritis.[24]

Neutrophil adhesion may play a particularly important role in diverse disorders associated with ischemia and reperfusion, including myocardial infarction, stroke, shock, organ transplantation, limb replantation, burns, and crush injuries. With prolonged ischemia there is damage to tissue from anoxia, but, paradoxically, further injury may occur after reperfusion. At least in some settings, this reperfusion injury appears to involve an inflammatory response.[25] Clearly the inflammatory system evolved long before reperfusion of ischemic organs was possible, so reperfusion injury probably represents an "accidental" triggering of the inflammatory response, not a mechanism of host defense and repair. The precise signals, such as oxidants, complement components, or cytokines, that trigger the inflammatory response during reperfusion have not been identified and may vary with the particular organ or disorder. The activation of leukocytes and endothelial cells during reperfusion results in neutrophil adhesion in capillaries producing plugging and further ischemia, or neutrophil adhesion to endothelium leading to the emigration of neutrophils with local edema formation, hemorrhage, and thrombosis. Because the CD11/CD18 complex is critically involved in these homotypic and heterotypic adhesive interactions of neutrophils, there is an opportunity to intervene therapeutically with blocking monoclonal antibodies directed at CD11b or CD18 (Figure 2).

Vedder and associates tested this novel approach in a rabbit ear model of isolated tissue ischemia-reperfusion.[26] They observed that the inhibition of leukocyte adherence with the CD18 monoclonal antibody 60.3—developed by Beatty and colleagues[27]—greatly attenuated neutrophil accumulation and associated endothelial and tissue injury after ten hours of warm ischemia followed by reperfusion. Furthermore, they found that this protection was the same whether the antibody was administered after ischemia occurred, but before reperfusion, or when administered before ischemia. These results indicate that leukocytes are important mediators of ischemia-reperfusion injury, that the leukocyte-mediated injury is in fact a reperfusion injury, and that it can be substantially attenuated by a CD18 monoclonal antibody administered at the time of reperfusion.

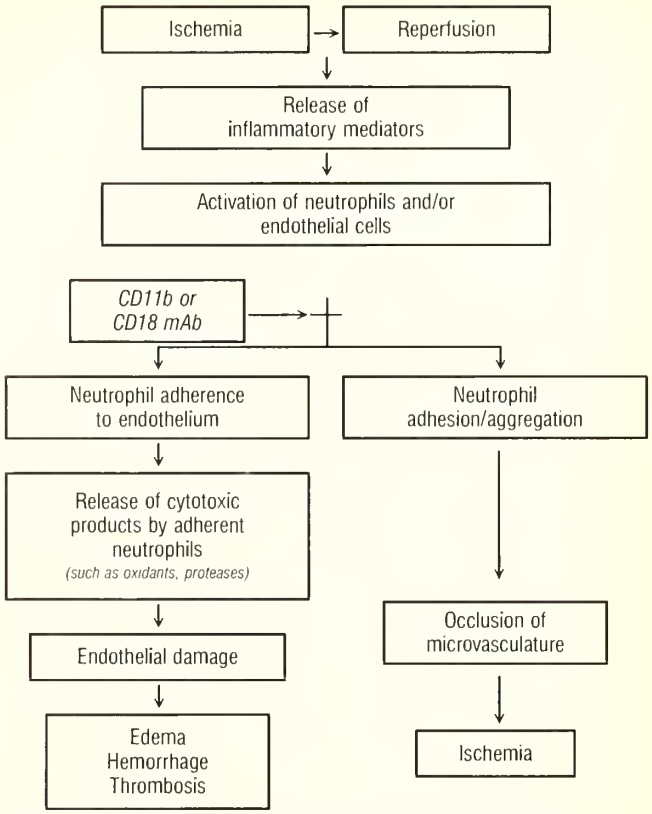

Figure 2.—The possible mechanism of action of CD11b or CD18 monoclonal antibody (mAb) is shown in preventing vascular and tissue injury after ischemia and reperfusion.

This approach was further tested in an animal model of hemorrhagic shock and resuscitation that may be relevant to the clinical syndrome of multiple organ failure. This syndrome is characterized by cardiovascular, pulmonary, central nervous system, hepatic, gastrointestinal, and renal dysfunction along with signs of generalized inflammation.[28,29] Vedder and colleagues hypothesized that shock (ischemia) followed by resuscitation (reperfusion) led to neutrophil adhesion in the microcirculation and the subsequent development of multiple organ failure. Administering the CD18 monoclonal antibody 60.3 before shock[30] or at the time of resuscitation[31] dramatically reduced the amount of vascular and tissue injury and improved survival in a rabbit model. These results were recently confirmed in a primate model in which a CD18 monoclonal antibody was administered at the time of resuscitation from hemorrhagic shock.[32] In control animals diffuse vascular injury developed, manifested by the capillary leak syndrome, requiring large volumes of fluid to maintain cardiac output. Visceral injury also developed in control animals in the form of gastritis observed by endoscopy. In contrast, animals treated with the CD18 monoclonal antibody required no fluids above maintenance to maintain cardiac output, and gastritis did not develop. Two of five control animals died, whereas all animals treated with monoclonal antibody 60.3 survived (Table 1).[32]

TABLE 1.—*Effect of CD18 Monoclonal Antibody Use in Hemorrhagic Shock**

Clinical Effect	*Animals*	
	Control (n = 5)	*60.3-Treated (n = 5)*
Fluid requirements†	259.8±225.7	9.6±8.8
Gastritis‡	5	0
Death, No.	2	0

*The CD18 monoclonal antibody 60.3 reduced vascular and tissue injury following hemorrhagic shock and resuscitation in primates (from Mileski et al[32]).

†Unit is milliliter per kilogram above maintenance required to maintain cardiac output over the first 24 hours.

‡Number of animals with the finding, as assessed by endoscopy.

These studies in the animal models show that CD18 monoclonal antibodies may prevent vascular and tissue damage by the inhibition of neutrophil adhesion after the generalized ischemia and reperfusion associated with shock and resuscitation. They also suggest that a similar approach may prevent or reduce the severity of multiple organ failure syndrome and prolong survival in trauma patients.

As dramatically shown by CD11/CD18-deficient patients, neutrophil adhesion to endothelium is necessary for host defense against bacterial infection at extravascular sites, raising the concern that even a transient inhibition of neutrophil adhesion might notably increase the susceptibility to and severity of bacterial infection. This possibility was examined in two models of infection in rabbits. The use of a CD18 monoclonal antibody did not increase mortality or infectious complications in animals with bacterial peritonitis,[33] and its use did not increase abscess formation at clinically relevant inocula of staphylococcal organisms in the skin.[34] These studies provide some reassurance that it may be safe to inhibit completely neutrophil adhesion for a limited period, even in trauma patients who are at risk of infection.

"Antiadhesion" therapy with monoclonal antibodies to the CD11/CD18 complex or its ligand ICAM-1 has been tested in a number of other models of ischemia-reperfusion and inflammatory or immune disorders (Table 2).[27,30-32,35-42] Other adhesion receptor-ligand interactions such as VLA-4 or VCAM-1 and the selectins are also possible targets for antiadhesion therapy. Possible therapeutic agents include murine or "humanized" monoclonal antibodies, peptides, soluble receptors, or small molecules (such as carbohydrates) that inhibit receptor-ligand interactions. Alternatively, drugs may be developed that disrupt the signal transduction pathways that are involved in the induction or activation of adhesion molecules.

TABLE 2.—*Antiadhesion Therapy in Experimental Models*

Model (Animal)	*Adhesion Protein*	*Reference*
Reperfusion injury		
Intestine (cat)	CD18	Hernandez et al, 1987[35]
Ear (rabbit)	CD18	Beatty et al, 1983[27]
Lung (rabbit)	CD18	Horgan et al, 1990[36]
Skeletal muscle (dog)	CD18	Carden et al, 1990[37]
Hemorrhagic shock (rabbit, primate)	CD18	Vedder et al, 1988[30]; Vedder et al, 1989[31]; Mileski et al, 1990[32]
Cerebral edema in bacterial meningitis (rabbit)	CD18	Tuomanen et al, 1989[38]
Myocardial infarction (dog)	CD11b	Simpson et al, 1990[39]
Autoimmune diabetes (mouse)	CD11b	Hutchings et al, 1990[40]
Allergic asthma (primate)	ICAM-1	Wegner et al, 1990[41]
Renal allograft rejection (primate)	ICAM-1	Cosimi et al, 1990[42]

In summary, there has been dramatic recent progress in our understanding of the cell and molecular biology, physiology, and clinical relevance of leukocyte-endothelial interactions. These insights may lead to the development of new therapies for a variety of human diseases.

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CASE HISTORIES—ONCOLOGY

#49803

The x-ray portals are ruled with purple ink,
  those doors through which the pulses pass,
destroying the destroyer.

Indelible, the lines frame that place
  where diseased cells lurk
sparing neither age nor gender.

Some walk the hall unnoticed,
  marks hidden by their clothes,
while others bear the grid on head or face

like the tribal tattoos of a different race.

#38594

Meant to bring forth life
  her womb now bears her death;
that crimson velvet pocket
  in which to carry treasure,
holds instead a dreadful counterfeit.

#32457

Pink and hairless as an embryo the ten-year-old
  lies on the x-ray table and stares back
into the black barrel of the massive machine.

Back in the child's room the stuffed toys wait,
  On the wall beside the bed
the artwork done the day before.

In the picture a big black cannon
  is aimed directly at the brightly crayoned house
With the smiling family standing in the yard.

And yet the child has also drawn
  a delicate pink flower growing
inside the cannon's threatening mouth.

#84573

She lies alone and still in the darkening room
and wonders why she cannot feel
the invader rearrange
the structure of her brain.
A blessing, she supposes, and yet
she would almost rather feel some pain
to help her understand that this is real
and not some dream that she will soon
be lying alone and still within her tomb.

ANNE KAVANAUGH©
Crozet, Virginia

Articles

Helmet Use Improves Outcomes After Motorcycle Accidents

MARGIE A. MURDOCK, RN, MSN, *and* KENNETH WAXMAN, MD, *Orange, California*

To determine the effects of motorcycle helmet use on the outcome of patients admitted to a Level I trauma center, we studied patient outcomes and demographic and epidemiologic variables of 474 patients injured in motorcycle collisions and treated at such a center over a 45-month period. Of those involved in a motorcycle collision, 50% were not wearing a helmet, 23% were wearing a helmet, and in 27% helmet use was unknown. Those who were wearing a helmet had fewer and less severe head and facial injuries, required fewer days on a ventilator, and sustained no serious neck injuries; fewer patients who wore helmets were discharged with disability, and hospital charges were lower. These data support the need for both increased public education regarding helmet use and mandatory helmet use legislation.

(Murdock MA, Waxman K: Helmet use improves outcomes after motorcycle accidents. West J Med 1991 Oct; 155:370-372)

Mandatory motorcycle helmet laws have been repealed or weakened in many states over the past several years. These repeals have been associated with an increased number of patients sustaining serious head injuries.[1-4] Public debate persists regarding the efficacy of helmet use in preventing death and disability. There is also argument that helmet use may be associated with an increased incidence of neck injury.

To address these issues, we examined the outcomes of patients admitted to our trauma center after motorcycle accidents. It was our goal to examine differences in outcome associated with helmet use.

Patients and Methods

The University of California Irvine Medical Center (UCIMC) is a 493-bed teaching hospital located in Orange County, California. It is one of three designated trauma centers and the only Level I center in the county. Countywide triage guidelines are used in the prehospital setting to identify and designate patients to be sent to a trauma center. The triage criteria are based on the mechanism of injury, vital signs, and other clinical findings. Triage decisions are the responsibility of base station physicians. Trauma registry information is obtained on all designated trauma center patients and entered into a computerized registry, from which the information for this study was derived. The following variables were analyzed: helmet use, age, sex, survival, duration of hospital stay, days in the intensive care unit, days on a ventilator, admission blood alcohol levels, neck injuries, disability status at discharge, insurance status, and hospital charges. In addition, the Abbreviated Injury Scale (AIS) was analyzed. This scale, based on anatomic findings, is used to assess and score injuries in six body regions using a scale of 1 (minor) to 6 (virtually unsalvageable injury).[5,6] Serious injuries receive an AIS score of 3 or above. This scoring was available on 296 patients, 205 without helmets and 91 with helmets.

The Student's *t* test or Fisher's Exact Test was used to evaluate the statistical significance of differences.

Results

Over a 45-month period, 3,941 designated trauma center patients were seen at UCIMC. In all, 474 (12%) were involved in a motorcycle collision. Of these, 236 patients (50%) were not wearing a helmet, 111 (23%) were wearing a helmet, and for 127 patients (27%) helmet usage was not documented. Most of the patients (449, or 95%) were male. The age range for the total motorcycle-riding group was from 4 to 66 years; the average age was 25. Patients wearing helmets averaged 26 years of age, and those not wearing them averaged 25 years. Of the helmet users, 97% were male, and 92% of nonhelmeted users were male. Those patients for whom helmet use was not documented were excluded from further analysis.

In the helmeted group, 4 patients (4%) had an AIS score in the head and neck category of 3 or more, and 39 patients (19%) in the nonhelmeted group had scores of 3 or more (Table 1). There was thus a statistically significant increased chance of sustaining a serious head injury when not wearing a helmet ($P < .001$).

The AIS category of facial injury scores ranged from 1 to 4. Those patients who were evaluated using the AIS system were reviewed for the incidence of facial injuries. In the helmeted population, 5 patients (5%) with facial injuries had

TABLE 1.—*Abbreviated Injury Scale (AIS) Scores for Head and Neck Injuries in Motorcycle Riders, by Helmet Use (n = 296)*

AIS Score*	Rider Wore Helmet, n = 91	Rider Did Not Wear Helmet, n = 205
1	14	54
2	7	29
3	3	8
4	1	11
5	0	19
6	0	1

*The scoring goes from 1 for least severe to 6 for most severe injury.

From the Department of Surgery, University of California Irvine Medical Center, Orange.
Supported in part by the Critical Care Foundation.
Reprint requests to Kenneth Waxman, MD, University of California Irvine Medical Center, 101 City Dr S, Orange, CA 92668.

ABBREVIATIONS USED IN TEXT

AIS = Abbreviated Injury Scale
UCIMC = University of California Irvine Medical Center

AIS scores of 1 or 2. In the nonhelmeted group, 36 patients (18%) with facial injury had AIS scores of 1 to 3 ($P < .01$).

One criticism used against wearing a helmet is that helmet use allegedly predisposes to neck injuries.[7] Ten patients sustained neck injuries, eight in the nonhelmeted group (3%) and two in the helmeted group (2%) ($P = .33$) (Table 2). None of these patients sustained permanent spinal cord injury or were discharged with a neurologic deficit. There were seven cervical spine fractures, six in the nonhelmeted group (3%) and one in the helmeted group (1%) ($P = .27$). In the nonhelmeted group, there was one injury to the larynx and one cricoid cartilage injury. In the helmeted group, one patient sustained a spinal cord contusion. Thus, helmet use was not associated with an increased risk of neck injury.

It is our trauma center policy to determine blood ethanol levels on all adult patients. Results were obtained on 103 (93%) of the helmeted patients and 228 (97%) of the nonhelmeted patients. Blood specimens were positive for ethanol in 32 of the helmeted patients (29%), and 23 (72%) of them had levels of 100 mg per dl (22 mmol per liter) or higher, which at the time was considered legally intoxicated in California. In the nonhelmeted group, 110 patients (47%) had a positive blood ethanol level, 75 of them (68%) having levels of 100 mg per dl or higher. The increased use of alcohol by nonhelmeted motorcyclists was statistically significant ($P < .005$).

In all, 152 patients were admitted to a critical care unit, 47 (42%) from the helmeted group and 105 (44%) from the nonhelmeted group ($P = .39$). In the helmeted group, 9 patients (8%) required ventilatory support, as did 46 patients (19%) from the nonhelmeted group. Thus, nonhelmeted patients were more likely to require ventilatory support ($P < .005$).

Most patients discharged with disability were from the nonhelmet-wearing group: 17 (7%) had substantially decreased cognitive functioning compared with 1 patient (1%) in the helmeted group ($P = .005$). Additional disabilities in the nonhelmeted group included four patients with leg amputations and one who sustained a cord contusion resulting in lower extremity weakness (Table 3). Four patients in the helmeted group had sustained additional disabilities, two with arm amputations, and one with a leg amputation, and one who was discharged with T-12 paraplegia.

A total of 20 patients died, 14 of whom were not wearing a helmet (6%) and 6 (5%) who were. The primary cause of death for 12 patients in the nonhelmeted group was the result of head injury (5%), and 2 died of chest injuries. One death (1%) in the helmeted group was the result of head injury, three were due to a transected aorta, and two were caused by intra-abdominal injury (Table 4). There was a significantly greater risk of death from head injury in nonhelmeted riders ($P < .05$).

TABLE 2.—*Neck Injuries Sustained in Motorcycle Riders, by Helmet Use (n = 447)*

*Neck Injury**	*Rider Wore Helmet, n = 111*	*Rider Did Not Wear Helmet, n = 236*
Cervical fracture	1	6
Cord contusion	1	0
Larynx	0	1
Cricoid	0	1
Total	3 (3%)	8 (3%)

*No patients were discharged with a neurologic deficit.

TABLE 3.—*Discharge Disabilities in Motorcycle Riders, by Helmet Use (n = 447)*

Disability	*Rider Wore Helmet, n = 111*	*Rider Did Not Wear Helmet, n = 236*
Head injury	1	17
Arm amputation	2	0
Leg amputation	1	4
Paraplegia or lower cord injury	1	1
Total	5 (5%)	22 (9%)

TABLE 4.—*Cause of Death in Motorcycle Riders, by Helmet Use (n = 447)*

Cause of Death	*Rider Wore Helmet, n = 111 No. (%)*	*Rider Did Not Wear Helmet, n = 236 No. (%)*
Head injury	1 (1)	12 (5)
Thoracic injury	3 (3)	2 (1)
Abdominal injury	2 (2)	0 (0)
Total	6 (5)	14 (6)

Hospital charges were collected on each patient after discharge from the hospital (professional fees not included). Charges for the helmeted population totaled $1,793,094; the average charge per patient was $16,154. The total hospital charge for the nonhelmeted group was $7,057,580, with the average charge per patient being $29,905. The insurance status of each patient was recorded at the same time as charges. A large percentage of patients in both groups was uninsured or had state or local indigent reimbursement that was below actual costs. Adequate reimbursement occurred for 53% of helmeted patients and 40% of the nonhelmeted group ($P < .05$). Adequate funding was considered the insurance grouping of private insurance (third-party payers; private insurance, health maintenance organizations, and Workers' Compensation) and CHAMPUS [Civilian Health and Medical Program of the Uniformed Services].

Discussion

Motorcycle riders are typically men in their mid-20s. Unless laws mandating helmet use are in place, these riders are not likely to wear helmets. Our data show that when riders not wearing helmets were brought to our trauma center after accidents, they had increased risks of serious head and facial injuries, prolonged hospital stays requiring ventilatory support, and either died of head injuries or were discharged with a neurologic deficit. These findings are consistent with those of previous reports.[3,8,9]

Our results also indicate that the use of a helmet does not increase the risk of sustaining a neck injury. There was no difference between the groups in the occurrence of neck injuries.

A significantly increased number of nonhelmeted patients sustained severe head injury resulting in decreased

cognitive functioning at the time of discharge. The long-term effect that these disabilities have on society in extended health care costs, custodial care, lost productivity, and emotional and financial burdens on families is impossible to determine accurately, but it is enormous.

The overall incidence of death was not statistically different between the groups. This may be somewhat misleading because it is likely that many motorcyclists not wearing a helmet sustained fatal head injuries and died immediately at the scene, were not taken to a trauma center, and were not included in this study. Helmeted riders may have survived more severe multisystem injury because of less severe head injuries, only to die of other injuries in the hospital.

The hospital charges for nonhelmeted patients were higher, yet were reimbursed at a lower rate than those of helmeted patients. We find it interesting that patients with CHAMPUS insurance had higher helmet use, perhaps indicating the success of instructions from the local naval base requiring all active duty personnel riding a motorcycle to wear a helmet both on and off duty.

Helmet use was effective in preventing death and disability from head injury in patients brought to our trauma center. There appeared to be no increased risk of neck injury involved with helmet use. This study and other published data support the need for increased public education regarding helmet use and mandatory helmet use legislation.[1-4,8,10] The justification for this includes not only individual safety but also the costs to society associated with nonhelmeted users' increased costs of hospital care and prolonged disability.

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Cardiac Dysfunction in Patients Seropositive for the Human Immunodeficiency Virus

MAJ JAMES E. JOHNSON, MC, USA; MAJ DAVID M. SLIFE, MC, USA; MAJ GREGG T. ANDERS, MC, USA; STEVEN R. BAILEY, MD; MAJ HERMAN M. BLANTON, MC, USA; COL C. KENNETH McALLISTER, MC, USA; *and* MAJ RICKY D. LATHAM, MC, USA, *Fort Sam Houston, Texas*

To confirm the presence of cardiac dysfunction in a group of patients seropositive for the human immunodeficiency virus with either dyspnea on exertion or a reduced anaerobic threshold, 9 patients with no history of opportunistic infection underwent exercise right-sided heart catheterization. When compared with 13 control patients previously exercised in the same manner, the patients showed elevated exercise pulmonary capillary wedge pressure (14.6 ± 3.3 mm of mercury versus 9.9 ± 3.3 mm of mercury; $P < .005$) and right atrial pressure (10.1 ± 2.1 mm of mercury versus 4.7 ± 3.2 mm of mercury; $P < .001$) at a similar exercise oxygen consumption and cardiac index. Of the 9 patients, 8 had at least 1 catheterization value outside the 95% confidence limits for the control group and 4 patients had multiple abnormalities. Values for blood CD4 lymphocytes were 0.2×10^9 per liter or more for 7 of the 9. One patient underwent endomyocardial biopsy with findings consistent with a cardiomyopathy. We conclude that cardiac disease may occur at any immunologic stage of human immunodeficiency virus infection. These observations suggest an effect of this disease on the heart.

(Johnson JE, Slife DM, Anders GT, et al: Cardiac dysfunction in patients seropositive for the human immunodeficiency virus. West J Med 1991 Oct; 155:373-379)

The morbidity and mortality associated with human immunodeficiency virus (HIV) infection once opportunistic infection has developed have been well described.[1,2] Morbidity at earlier stages of HIV infection is less well understood. Although several cases of heart disease have been reported in patients with the acquired immunodeficiency syndrome (AIDS),[3-14] little has been written about cardiac dysfunction in HIV-infected patients without overt opportunistic infection. Levy and co-workers have described echocardiographic abnormalities in 7 of 25 patients with "pre-AIDS."[15] At our own institution, exercise testing of HIV-seropositive men revealed a subgroup with evidence suggesting cardiac limitation.[16,17] Of 32 patients who were evaluated, 13 had some degree of dyspnea on exertion. No evidence of opportunistic infection was found on history, physical examination, or chest roentgenogram. In addition, nearly all underwent bronchoalveolar lavage, gallium scanning, and pulmonary function testing with measurement of the single-breath diffusing capacity of the lungs for carbon monoxide with no evidence found for opportunistic pulmonary infection. Of the 32 patients, 9 had a ventilatory anaerobic threshold that was less than the 95% confidence interval for the HIV-seronegative control group. This subgroup showed a low mean maximum oxygen consumption, an increased slope of the relationship of the heart rate to oxygen consumption, and a mild tachypnea during exercise. These findings are most consistent with a limitation in oxygen delivery during exercise. Because deconditioning may be difficult to differentiate from cardiac disease by noninvasive exercise testing,[18] we sought further confirmation of cardiac dysfunction by invasive exercise testing. Weber and Janicki have shown that the lower the maximal oxygen consumption ($\dot{V}O_2$ max) and anaerobic threshold values are in patients with cardiomyopathy, the greater the likelihood is that they will manifest elevated filling pressures and reduced cardiac output responses to exercise.[19] We therefore compared the submaximal exercise response of a group of HIV-seropositive men with the response of a group of control patients previously exercised in our cardiac catheterization laboratory.

Patients and Methods

Study Population

Patients seropositive for HIV were eligible for the study. An effort was made to recruit persons with either of the following:

- Symptoms of dyspnea on exertion;
- A ventilatory anaerobic threshold of less than 46.2% of predicted $\dot{V}O_2$ max (one-tailed 95% confidence limit for normal young men in our laboratory), a $\dot{V}O_2$ max of less than 80% of predicted, or both.

Patients were excluded for the following reasons:

- A preliminary evaluation revealed overt opportunistic infection;
- A patient was known to have preexisting cardiac or pulmonary disease;
- Other complicating medical disorders were present that would preclude maximal exercise testing.

The study was reviewed and approved by the institutional review board. Informed consent was obtained from all subjects.

From the Pulmonary Disease/Critical Care Service (Drs Johnson, Anders, and Blanton), Cardiology Service (Drs Slife, Bailey, and Latham), and Infectious Disease Service (Dr McAllister), Brooke Army Medical Center, Fort Sam Houston, Texas.

The opinions or assertions contained herein are the private views of the authors and are not to be construed as reflecting the opinion of the Department of the Army or the Department of Defense.

Reprint requests to Maj James E. Johnson, MC, HSHE-MDP, Brooke Army Medical Center, Fort Sam Houston, TX 78234-6200.

ABBREVIATIONS USED IN TEXT

AIDS = acquired immunodeficiency syndrome
HIV = human immunodeficiency virus
PCW = pulmonary capillary wedge
$\dot{V}CO_2$ = carbon dioxide production
$\dot{V}_E$ = expired ventilation
$\dot{V}O_2$ = oxygen consumption
$\dot{V}O_2$ max = maximum oxygen consumption
WR = Walter Reed [classification system]

Evaluation Protocol

Each patient had a chest roentgenogram, an electrocardiogram, a complete blood count, and a forced vital capacity. The forced vital capacity maneuver was performed with a SensorMedics Horizon System (SensorMedics, Inc, Anaheim, California). Normal standards were those of Morris and co-workers.[20] On separate days a cardiopulmonary exercise test using upright bicycle ergometry and a supine exercise right-sided heart catheterization were done. The patient was restaged by the Walter Reed (WR) classification if this had not been done within the previous six months. Briefly, this classification is as follows[21]:

WR1—No signs or symptoms, CD4 lymphocyte count 0.4×10^9 per liter (400 per μl) or more;

WR2—Adenopathy present, CD4 count 0.4×10^9 per liter or more;

WR3—CD4 count less than 0.4×10^9 per liter, normal delayed hypersensitivity;

WR4—CD4 count less than 0.4×10^9 per liter, partial cutaneous anergy;

WR5—CD4 count less than 0.4×10^9 per liter, complete cutaneous anergy or oral thrush present;

WR6—Opportunistic infection present.

Noninvasive cardiopulmonary exercise test. The patients were exercised on an electromechanically braked bicycle ergometer (Mihnhardt KEM-3, Banik, Holland) on a protocol that began with two minutes of rest, three minutes of pedaling at 0 watts, and then pedaling at a workload that increased by 25 watts per minute in increments until exhaustion. Arterial oxygen saturation was measured noninvasively by pulse oximetry (Pulse Oximeter NIOD, Nellcor Incorporated, Hayward, California). Expired gas was analyzed by means of a SensorMedics 4400TC (SensorMedics, Inc). With this system, the exhaled volume was measured by means of a digital volume transducer. The expired oxygen concentration was measured by a Zirconium Furnace analyzer and the carbon dioxide concentration by an infrared analyzer. The expired gas was sampled continuously at the level of the mouthpiece for breath-by-breath analysis. Calibration of the volume measurement was accomplished at several flow rates by means of a 3-liter syringe. Gas analyzers were calibrated with ambient air and two standard gas mixtures. Data were processed on line by a microprocessor and expressed in one-minute averages for heart rate, oxygen consumption ($\dot{V}O_2$), carbon dioxide production ($\dot{V}CO_2$), expired ventilation ($\dot{V}_E$), respiratory frequency, and tidal volume. The ventilatory anaerobic threshold was determined by examining 15-second average $\dot{V}_E/\dot{V}CO_2$ and $\dot{V}_E/\dot{V}O_2$ ratios versus time curves. The $\dot{V}O_2$ at the time when the $\dot{V}_E/\dot{V}O_2$ ratio rose while the $\dot{V}_E/\dot{V}CO_2$ ratio remained relatively unchanged was taken as the ventilatory anaerobic threshold. The maximum predicted heart rate was calculated as 220 minus the age in years. The maximum voluntary ventilation was estimated as the forced expiratory volume in one second times 40.[16] The formulas of Wasserman and colleagues were used for the predicted $\dot{V}O_2$ max.[22] The data were compared with those of 22 HIV-seronegative controls exercised for the previous study.[16]

Exercise right-sided heart catheterization. Patients were brought to the Cardiac Catheterization Laboratory in an unsedated state with no medicines. After local anesthesia was administered with 2% lidocaine, a small venotomy was made in the right antecubital area that allowed a 7F balloon-tipped, thermodilution catheter to be introduced into the vein and advanced to the right heart chambers under fluoroscopic guidance. Pressure transducers were placed at the midaxillary level and opened to atmosphere to establish the zero baseline. Pressures in the pulmonary capillary wedge (PCW), pulmonary artery, right ventricular, and right atrial positions were recorded sequentially on a strip chart. Pulmonary artery blood was drawn for oxygen saturation determinations. Thermodilution cardiac output was determined using 10 ml of iced saline solution. A mean of the results of three injections was used for the cardiac output at rest and that of two injections was used with exercise. The patient's feet were then raised into the bicycle ergometer and again a mean PCW, mean pulmonary artery, and mean right atrial pressure were recorded. The patient was then exercised at 50 watts. After a steady state was verified by a stable heart rate, all patients were exercised a full five minutes. During steady-state exercise, the mean right atrial pressure, mean PCW pressure, and pulmonary arterial systolic and diastolic pressures were recorded. The mean of each of these pressures over the respiratory cycle was used. Thermodilution cardiac output and mixed venous oxygen saturation level were also obtained. The cardiac index and stroke volume index were calculated from these values.

Control Group

The results of exercise right-sided heart catheterization were compared with those of a group of 13 control patients exercised in our catheterization laboratory over the past 15 years. These 13 were all studied because of atypical chest pain syndromes. All were active-duty military men. All were found to have normal coronary arteries and left ventricular ejection fractions. One had ergonovine challenge testing without angiographic evidence of coronary artery spasm. None had evidence of hypertension or valvular heart disease. All were exercised at 50-watt workloads, and the present study was designed to match the protocol used for the controls. Of the 13, 4 were known to be HIV-seronegative and 4 were exercised before the onset of the AIDS epidemic; the HIV status of the other 5 was unknown. Three of the control

TABLE 1.—*Demagraphic Characteristics of Patients and Cantrols Undergaing Exercise Right-sided Heart Catheterization**

Demagraphic	*Cantrols, n = 13*	*Patients, n = 9*
Age, years.	35.1±10.3	33.6±5.3
Height, cm (in) . .	178.8±6.1 (70.4±2.4)	177.3±5.6 (69.8±2.2)
Weight, kg (lb) . .	86.0±11.1 (189.5±24.4)	80.5±12.9 (177.4±28.5)

*Measurements are given as the mean ± 1 SD.

TABLE 2.—*Selected Data From Patients Undergoing Right-sided Heart Catheterization*

Patient	WR Class*	CD4 Count, $\times 10^9$/liter (/μl)	Hemoglobin, grams/liter†	Smokes Cigarettes	Dyspnea on Exertion	Regular Aerobic Training	Zidovudine
1	4	0.3 (267)	127	No	Yes	Yes	Yes
2	1	0.9 (874)	156	Yes	Yes	Yes	No
3	1	0.5 (480)	148	Yes	Yes	Yes	No
4	1	0.6 (598)	140	Yes	Yes	Yes	No
5	1	0.9 (911)	157	No	No	Yes	No
6	2	0.5 (522)	140	No	No	Yes	No
7	5	0.1 (129)	135	No	Yes	No	No
8	5	0.1 (127)	130	No	Yes	Yes	Yes
9	2	0.8 (750)	150	No	Yes	Yes	No

*Walter Reed staging classification for HIV infection. See text for brief description.
†To convert to conventional units of grams/dl, multiply by 0.1.

TABLE 3.—*Upright Bicycle Ergometer Exercise Results*

Patient	Heart Rate, sec^{-1} Rest	Heart Rate, sec^{-1} Max (% Pred)	Blood Pressure, Mean mm of mercury Rest	Blood Pressure, Mean mm of mercury Max Exer	$\dot{V}O_2$ max, ml/kg	$\dot{V}O_2$ max, % Pred	Ventilatory Anaerobic Threshold % Pred $\dot{V}O_2$ max,	Max Work, watts	Max $\dot{V}_E$, liters/min (% MVV)
1	105	190 (101)	90	113	28.8	74.4	39.3	200	105 (67.3)
2	70	185 (92)	97	113	40.2	92.0	41.3	225	108 (69.7)
3	107	170 (92)	91	114	23.3	63.8	37.6	175	114 (71.3)
4	105	180 (96)	91	115	32.5	87.6	44.4	200	143 (92.2)
5	74	144 (77)	106	133	28.4	69.9	34.4	175	72 (50.3)
6	100	175 (95)	68	100	30.9	100.0	54.0	200	86 (58.9)
7	82	159 (85)	70	105	27.9	58.2	25.2	150	108 (64.3)
8	75	172 (96)	105	127	45.8	122.0	65.6	250	129 (76.7)
9	63	160 (85)	93	128	20.7	70.3	38.2	200	103 (69.1)

Exer = exercise, Max = maximum, MVV = maximum voluntary ventilation, Pred = predicted, Rest = resting, $\dot{V}_E$ = expired ventilation, $\dot{V}O_2$ max = maximal oxygen consumption

group were studied by cardiologists involved in the present study (D.M.S., R.D.L.), and two were studied concurrently with the HIV-infected patients.

The procedure used for the patients in our study differed from that used for the controls only as follows: Expired gas analysis was accomplished by the SensorMedics 4400TC as for our patients, but a five-minute Douglas bag collection was used for the controls at rest and during steady-state exercise. In this group, the expired volume was measured using a spirometer and corrected to body temperature, ambient pressure, and for water vapor saturation. The $\dot{V}O_2$ and $\dot{V}CO_2$ were calculated after measuring expired concentrations by means of a mass spectrometer (Perkin Elmer Inc, Pomona, California). Thermodilution cardiac output measurements were available for only 7 of the 13 controls. These 7 had been studied in an identical manner to the HIV-infected patients; therefore, cardiac output and measurements derived from it are compared only with the data of these 7.

Statistical Analysis

When applicable, data are given as the mean plus or minus one standard deviation. The unpaired Student's *t* test was used to compare various measurements between the patients and the control group. To identify individual patients who had abnormal results for various tests, the confidence intervals for the *t* distribution were used. The one-tailed 95% level was used unless otherwise indicated because the a priori hypothesis was that the patients would have higher filling pressures and lower systolic values (such as cardiac output and stroke volume) than the controls.

Results

Ten HIV-seropositive men were interviewed for the study, and all but one agreed to participate. The one who refused was an asymptomatic 27-year-old African-American man immunologically staged as WR5. Demographic features of the other 9 patients are given in Table 1 and are compared with those of 13 controls undergoing exercise right-sided heart catheterization. There was no significant difference in age, height, or weight between the two groups. In the patient group, 6 were white and 3 were African American; 11 in the control group were white, and 2 were African American. Three of the patients and two of the controls were smokers. Table 2 shows selected data for individual patients. All but one of the patients were military service members, and five of the nine had participated in our previous exercise study.[16]

Patient 6 had an early repolarization pattern on an electrocardiogram. Patients 4 and 8 had minor ST segment and T wave changes. Otherwise, the patients' electrocardiograms were normal. All patients had normal spirometry values. The chest roentgenograms were all normal except that of patient 7, which showed a mild increase in interstitial markings. Patients 1, 2, 4, 7, and 9 underwent bronchoalveolar lavage for another research protocol, with no evidence of opportunistic pulmonary infection noted on examination of the fluid.

Noninvasive cardiopulmonary exercise test. Data from the upright noninvasive exercise test are given in Table 3. All but one patient exercised to 85% or more of his maximum predicted heart rate. Seven of the nine patients had ventila-

TABLE 4.—*Supine Right-sided Heart Catheterization After Submaximal Exercise*

Patient	Right Atrial Pressure, mm of mercury		Pulmonary Artery Pressure, mm of mercury		Pulmonary Capillary Wedge Pressure, mm of mercury	
	Resting	Exercise	Resting	Exercise	Resting	Exercise
1	1	12*	14	26	3	8
2	7	7	18	23	11	11
3	6	10	16	27	9	16*
4	8	10	18	20	10	13
5	4	8	13	22	8	16*
6	7	11*	17	28	9	18†
7	3	8	16	18	8	16*
8	8	12*	18	23	10	15
9	17†	13†	24†	26	16†	18†
Mean	6.8	10.1‡	17.1§	23.7	9.3	14.6‖
SD	4.5	2.1	3.1	3.4	3.4	3.3
Control (n = 13)						
Mean	4.4	4.7	13.8	21.1	7.7	9.2
SD	2.1	3.2	2.8	5.5	2.7	3.3

*Value above the 1-tailed 95% confidence interval for controls.
†Value above the 1-tailed 99% confidence interval for controls.
‡$P < .001$ compared with controls.
§$P < .01$ compared with controls.
‖$P < .005$ compared with controls.

tory anaerobic threshold values of less than the one-tailed 95% confidence interval for our laboratory (46.2% of the predicted $\dot{V}O_2$ max). Five of the nine patients exercised to less than 80% of the predicted $\dot{V}O_2$ max. All had a normal rise in blood pressure with exercise. Patient 4's $\dot{V}_E$ exceeded 80% of maximum voluntary ventilation at maximum exercise. None had a 2% or greater reduction in arterial oxygen saturation. Three patients had a ventilatory frequency at maximum exercise of greater than 50 (patient 3, 56 per minute; patient 7, 51 per minute; patient 9, 55 per minute). Only two of the patients had test results that were normal in every respect (patients 6 and 8). Both had a history of exceptional fitness antedating their diagnosis of HIV infection. Patient 8 had successfully completed a marathon 18 months before the study. Despite his level of fitness, this patient had dyspnea on exertion during the six-month interval before the study.

Exercise right-sided heart catheterization. Table 4 shows pressure data from the right heart studies. As a group, the patients had similar right atrial and PCW pressures at rest, but these pressures were significantly higher in patients with exercise than they were in controls. The pulmonary artery pressure was higher in the patients than in the controls, but this only reached statistical significance at rest. The mean heart rate, $\dot{V}O_2$, and oxygen pulse (milliliters of oxygen consumed per cardiac cycle) were similar at rest and exercise in the two groups, but the slope of the heart rate versus the $\dot{V}O_2$ relationship was significantly steeper for the patients than the controls (Table 5).

Table 6 shows thermodilution cardiac output data. As a group, there was no difference between patients and controls in cardiac index or stroke volume index with rest or exercise. The exercise factor calculated as the rise in cardiac output per

TABLE 5.—*Supine Right-sided Heart Catheterization Results After Submaximal Exercise*

Patient	Heart Rate, cycles/min		$\dot{V}O_2$, ml/min		Oxygen Pulse, ml/cycle		Heart Rate vs $\dot{V}O_2$ Slope, cycles/liter
	Resting	Exercise	Resting	Exercise	Resting	Exercise	
1	76	147*	200	1,262	2.6	8.6	67
2	59	110	250	1,152	4.2	10.5	57
3	61	104	240	880	3.9	8.5	67
4	78	143*	400†	1,418	5.1	9.9	64
5	76	103	240	980	3.2	9.5	36
6	61	111	250	1,100	4.1	9.9	58
7	74	119	250	1,000	3.4	8.4	60
8	67	97	300	1,000	4.5	10.3	43
9	55	123	300	995	5.5	8.1	98*
Mean	67	117	270	1,087	4.1	9.3	61‡
SD	9	18	58	167	0.9	0.9	17
Control (n = 13)							
Mean	72	108	289	1,127	4.1	10.3	44
SD	16	12	59	289	0.7	2.0	17

$\dot{V}O_2$ = oxygen consumption

*Value above the 1-tailed 99% confidence interval for controls.
†Value above the 1-tailed 95% confidence interval for controls.
‡$P < .025$ compared with controls.

TABLE 6.—*Supine Right-sided Heart Catheterization Results After Submaximal Exercise*

Patient	Cardiac Index, liters·min⁻¹·m⁻²		Stroke Volume Index, ml·cycle⁻¹·m⁻²		Exercise Factor, ml/dl $\dot{V}O_2$
	Resting	Exercise	Resting	Exercise	
1	4.1	10.7	54.1	72.8	1,151
2	3.0	6.2	51.3	55.9	676
3	2.2*	5.8	35.9	55.6	1,078
4	4.7	6.5	59.8	45.3*	373*
5	3.6	6.8	47.1	65.7	841
6	4.9	11.1	79.7	100.5	1,341
7	3.3	7.4	44.0	61.8	973
8	3.6	6.7	54.3	68.7	842
9	1.9*	4.6	34.8	37.5†	892
Mean	3.5	7.3	51.2	62.7	907
SD	1.0	2.2	13.6	18.1	280
Control (n = 7)					
Mean	3.5	6.7	47.3	63.0	877
SD	0.6	1.3	7.9	6.6	231

$\dot{V}O_2$ = oxygen consumption

*Value less than the 1-tailed 95% confidence interval for controls.
†Value less than the 1-tailed 99% confidence interval for controls.

deciliter rise in $\dot{V}O_2$ was calculated and found to be similar between the two groups.

Comparing the patients' data with those of the controls, the mean arterial oxygen saturation was similar at rest (0.97 ± 0.017 versus 0.97 ± 0.013) and exercise (0.97 ± 0.016 versus 0.97 ± 0.013). The mixed venous saturation was significantly lower at rest in the patient group (0.743 ± 0.037 versus 0.782 ± 0.035; $P < .01$) and the arterial-venous oxygen content difference (4.5 ± 0.9 ml per dl versus 3.9 ± 0.7 ml per dl) was higher, although the latter did not reach statistical significance. Neither the mixed venous saturation nor the arterial-venous oxygen saturation was significantly different with exercise. Although the mean hemoglobin concentration of the patients was somewhat lower than that of controls (143 ± 11 grams per liter versus 154 ± 14 grams per liter; difference not significant by two-tailed test), the greatest derangements in resting mixed venous saturation and difference in arterial-venous oxygen content were seen in patients with normal hemoglobin levels.

A review of the patients' data individually revealed that one patient had no findings outside the 95% confidence limits but eight did. Four of these eight had several abnormalities: Patient 9 had high resting right atrial and PCW pressures with a low cardiac index and mixed venous saturation and a widened difference in arterial-venous oxygen. With exercise, his heart rate response was high relative to his $\dot{V}O_2$ rise and his stroke volume index was greatly reduced with exercise compared with controls. His filling pressures remained abnormally high during exercise. It is of interest that this patient had been exercised noninvasively in our laboratory a year previously before he became symptomatic with dyspnea on exertion. At that time his $\dot{V}O_2$ max and ventilatory anaerobic threshold were 118% and 51% of predicted $\dot{V}O_2$ max, with these values dropping to 70.3% and 38.2%, respectively, at the time of the present study. Because of these findings, an echocardiogram was done that showed mild left ventricular dilation and hypokinesis. An endomyocardial biopsy specimen revealed myofibrillar loss and atrophy and interstitial fibrosis consistent with cardiomyopathy without any acute inflammation (Figure 1).

Patient 3 had a low cardiac index and mixed venous saturation at rest with a widened difference in arterial-venous oxygen. With exercise, his PCW pressure was high. His heart rate versus $\dot{V}O_2$ relationship was close to the 95% confidence limit. Patient 6, despite his well-preserved exercise tolerance, had a wide resting arterial-venous oxygen difference and significantly elevated right atrial and PCW pressures with exercise. Patient 4 had a normal modest rise in his filling pressures with exercise but failed to augment his cardiac index normally. His stroke volume actually fell with exercise. His exercise heart rate was considerably increased and the exercise factor reduced.

Discussion

The current data provide support that low ventilatory anaerobic threshold and $\dot{V}O_2$ max values are due to cardiac disease in HIV-infected patients who appear to be free of obvious opportunistic infection.

As a group, the patients exercised at the same submaximal workload as the controls and reached a similar $\dot{V}O_2$ and cardiac index response. They did this, however, at higher filling pressures for both the right and left ventricles. This finding has been described previously as a sign of cardiac disease.[19,23,24] Increased PCW pressure with exercise has been the most extensively studied [23] and has been found to be a more sensitive indicator of cardiac dysfunction than the cardiac output response. An inappropriate rise in afterload may also produce an increased PCW pressure with exercise, but this should be accompanied by a hypertensive response, a finding not noted in any of these patients. Five of our patients had exercise PCW pressures above the 95% or 99% confidence limits. Overall, eight of the patients had cardiac catheterization values outside the 95% confidence intervals—four with multiple abnormalities. The occurrence of several abnormalities, even modest ones, in the same patient is unlikely to be due to chance alone.

The present study was designed only to document invasively the presence of cardiac dysfunction with exercise in this largely symptomatic population of patients (having dyspnea on exertion). Discovering the cause of this dysfunction

was not our intention, but certain observations can be made. Certainly the valvular and atherosclerotic causes of heart disease seen so commonly in the United States are unlikely in this group of young men lacking a history of chest pain and having normal findings on physical examinations and electrocardiograms. The endomyocardial biopsy specimen from patient 9 showed changes consistent with a cardiomyopathy. This pattern is not specific for a primary cardiomyopathy but can be due to chronic ischemia or abuse of cocaine.[25] None of the patients admitted to drug abuse, however. Given the lack of evidence for other forms of heart disease and the biopsy findings in patient 9, cardiac muscle disease appears to be the most likely explanation for the cardiac dysfunction.

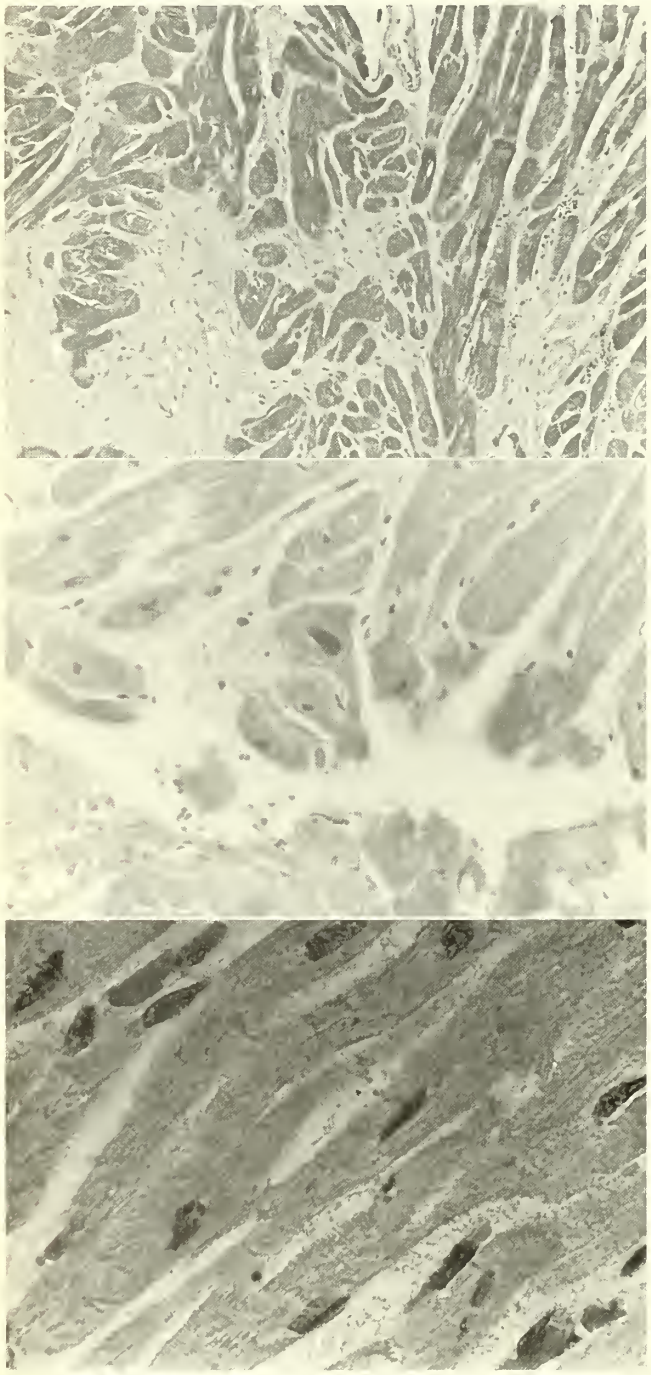

Figure 1.—Photomicrographs of an endomyocardial biopsy specimen taken from patient 9 show myofibrillar loss and atrophy as well as interstitial fibrosis (top, Masson-Trichrome stain, original magnification × 100; center, hematoxylin-eosin stain, original magnification × 400). Bottom, normal myocardium is shown for comparison.

Our own data complement those of Levy and colleagues,[15] their study being primarily anatomic while ours was functional. They performed echocardiograms on 60 HIV-infected patients, 35 with AIDS and 25 with pre-AIDS. Echocardiographic abnormalities were found in 14 and 7 of these patients, respectively. The most common finding was left ventricular dilatation or hypokinesis, and the findings as a whole were more severe in the group with AIDS. Unlike our study, they found cardiac abnormalities to be uncommon in patients with CD4 lymphocyte levels greater than 0.1×10^9 per liter (100 per μl). All of our patients had CD4 levels of greater than 0.1×10^9 per liter.

Previous studies of heart disease in HIV-infected persons have focused primarily on the AIDS population. Cardiac disease is common in this group, occurring in 29% to 52% of some series.[3-5] Opportunistic infection of the heart with *Mycobacterium avium-intracellulare*, *Cryptococcus* species,[6,7] cytomegalovirus,[5] and *Aspergillus fumigatus*[8] has been described. In addition, an idiopathic dilated cardiomyopathy or myocarditis[5,9-14] has been observed. Anderson and associates reviewed 71 consecutive autopsies of patients with AIDS and found myocarditis in 37 (52%).[5] In most, the cause remained unknown without direct evidence of cardiac opportunistic infection. Several possible explanations were considered as follows: a direct cytolytic effect of HIV itself on the myocytes; an immune-mediated "innocent bystander destruction," as proposed by Ho and co-workers for neurologic cell damage in AIDS-associated subacute encephalitis[26]; or an unrecognized opportunistic infection with cytomegalovirus, Coxsackie B virus, or another organism.

It is our hypothesis that the cardiac dysfunction seen in our own population represents either or both an early stage of the cardiomyopathy or myocarditis described in the AIDS population. Because opportunistic infection (at least in the lung) is unusual in patients with CD4 counts of 0.2×10^9 per liter or more[27] and because many of our patients had well-preserved CD4 counts, opportunistic cardiac infection seems unlikely as a cause for our findings. Therefore, our data favor a more direct effect of HIV itself as postulated by Anderson and associates[5] and discussed earlier.

The role of noninvasive exercise testing in detecting cardiac disease in these patients remains to be determined. It has been shown to be useful in identifying patients with *Pneumocystis carinii* pneumonia if exercise arterial blood gas values are monitored.[28] Certainly it was useful in identifying a population likely to have cardiac abnormalities on exercise right-sided heart catheterization in this study, but two of eight patients with such abnormalities had normal results of noninvasive exercise tests. Exercise function has been preserved in some patients with mild cardiomyopathies.[19] Therefore, it is likely that some combination of exercise testing and imaging techniques will be necessary to diagnose cardiac disease as the cause of symptoms in HIV-infected patients.

There are some limitations to the present study. First, the small number and careful selection of patients make it impossible to draw a conclusion about the frequency of cardiac disease in this population. Second, the relative contribution of systolic and diastolic dysfunction to the elevation in filling pressures cannot be determined without further studies such as left ventricular function curves or echo Doppler evaluation. Finally, most of the control group were evaluated before

the current study. This limitation is mitigated by the extensive experience with exercise hemodynamics in our laboratory and by our specifically designing the present study to match the protocol under which previous controls were exercised.

Currently, cardiac disease is the cause of death in only a few AIDS patients. As survival in HIV-infected patients increases due to improved treatment of opportunistic infection, it is likely that the incidence of symptomatic heart disease will increase. Further studies are needed to delineate the cause(s) of this disorder. If the human immunodeficiency virus itself is implicated by such techniques as immunohistochemistry or in situ hybridization, trials of antiretroviral therapy may be warranted in symptomatic HIV-infected patients with evidence of heart disease.

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Articles

Patterns of Primary Care of Patients Infected With Human Immunodeficiency Virus

MARJORIE D. WENRICH *and* PAUL G. RAMSEY, MD, *Seattle, Washington*

To determine the patterns of care of patients infected with the human immunodeficiency virus (HIV), data from 2 sources were analyzed. Initial data obtained from the Washington State HIV/Acquired Immunodeficiency Syndrome (AIDS) Epidemiology Unit indicate that 46% of patients with class IV AIDS were seen by physicians who reported fewer than 5 patients with AIDS, and 68% of all Washington physicians who reported treating patients with AIDS have reported only 1 patient. Subsequent data obtained from a questionnaire distributed in 4 Northwest states suggest that 74% of primary care internists and 73% of family practitioners have some experience in caring for patients with HIV infection, but most of these physicians report fewer than 6 patients in the past 2 years. Although most providers seeing large numbers of HIV-infected patients in their practices were based in the region's major metropolitan area, 59% of the internists and 55% of the family practitioners surveyed outside of the metropolitan area had seen at least 1 HIV-infected patient in their practices. These results suggest that primary care physicians with relatively little experience treating HIV infection are providing care for a large number of HIV-infected persons. Further study is needed to determine the extent and quality of care provided.

(Wenrich MD, Ramsey PG: Patterns of primary care of patients infected with human immunodeficiency virus. West J Med 1991 Oct; 155:380-383)

In the next five to ten years, primary care physicians probably will play an increasingly important role in the identification and care of patients infected with the human immunodeficiency virus (HIV).[1-4] This increased role has been predicted based on an increase in the number of patients with symptomatic HIV infection and changing patterns of health care provision, including a shift in the principal care setting from inpatient to outpatient.[5] In addition, advances in medical therapy, such as the early use of zidovudine, are resulting in increased longevity among HIV-infected patients.[6-9] Increasingly, the acquired immunodeficiency syndrome (AIDS) may be redefined as a chronic disease with periods of acute infection interspersed with periods of maintenance care.[5,10,11]

The willingness and preparedness of primary care physicians to assume an increased role in the identification and management of patients with or at risk for HIV infection have not been established. Concern or fear associated with the treatment of HIV-infected patients by health care professionals has been well documented,[12,13] and stress and fatigue associated with treating AIDS patients are additional factors that may deter physicians from accepting patients with HIV infection.[14] A survey conducted in Los Angeles in 1985 indicated that many physicians believed that they lacked experience and knowledge to treat AIDS,[15] and data from a telephone survey conducted in California in 1984 suggest a lack of necessary knowledge and skills related to AIDS among primary care physicians.[16]

Few data are available concerning the patterns of primary care of patients with HIV infection. In the California telephone survey, about 10% of physicians interviewed in counties with major metropolitan centers had patients from their practices diagnosed as having AIDS by Centers for Disease Control (CDC) criteria, and 4% of those practicing in counties without major metropolitan centers had patients from their practices diagnosed as having AIDS.[16] Surveyed physicians expressed an interest in the establishment of special clinics for AIDS patients staffed by physicians with particular expertise in this disease. Since this survey was completed, the number of patients with AIDS has increased dramatically, and more primary care physicians may have experience with HIV-infected patients than were recognized previously.

What are the current patterns of care in different communities for patients with HIV infection? Is the care of HIV-infected patients concentrated in the practices of a small number of physicians in the same manner that a few hospitals are treating a large number of patients with AIDS?[17] To address these questions, data were recently obtained to assess the patterns of care for HIV-infected patients in the Pacific Northwest.

Methods

To ascertain the distribution of reported patients with AIDS among physicians in all specialties, data were obtained from the Washington State HIV/AIDS Epidemiology Unit concerning the number of physicians in Washington State who reported CDC class IV AIDS cases between January 1982 and June 30, 1989. The HIV/AIDS Epidemiology Unit, which is the state's surveillance unit for AIDS, uses a number of active and passive methods for collecting case reports. These include record review, death certificate review, and outside audit of physicians' offices. After obtaining these data, in July 1989 a survey was mailed from the University of Washington to 500 randomly selected internists and family practitioners in Washington, Alaska, Montana, and Idaho who were identified through University of Washington clinical faculty records and telephone directories to determine patterns of primary care throughout the region.

From the Department of Medicine, University of Washington School of Medicine, Seattle. Dr Ramsey is a Henry J. Kaiser Family Foundation Faculty Scholar in General Internal Medicine. The views expressed herein are those of the authors and do not necessarily reflect the views or policies of the Henry J. Kaiser Family Foundation.

Reprint requests to Paul G. Ramsey, MD, Department of Medicine, RG-20, University of Washington, Seattle, WA 98195.

ABBREVIATIONS USED IN TEXT

AIDS = acquired immunodeficiency syndrome
CDC = Centers for Disease Control
HIV = human immunodeficiency virus
SD = standard deviation

A cover letter that accompanied the questionnaire described the survey as an attempt to obtain information about the practice patterns of primary care physicians and medical subspecialists in the Northwest. Different questionnaires were mailed to internists and family practitioners.

The questionnaire to internists contained questions about physicians' practice characteristics, including the percentage of a physician's patients for whom the physician serves as the principal physician; the percentage of the physician's patients for whom only subspecialty care is provided and for whom general care is not provided; the percentage of the physician's professional patient-related activities devoted to general internal medicine practice, subspecialty practice, and non-internal medicine specialty practice; and the year of graduation from medical school. Information was obtained concerning the state of practice and whether the physician resided or practiced in the major metropolitan area in the region (Seattle and Tacoma) or outside of this metropolitan area. To determine patterns of care, physicians were asked to identify the approximate number of patients they had treated in the past two years in several categories, including HIV infection with or without AIDS.

The questionnaire to family practitioners contained the same questions concerning patterns of care. Family practitioners were not asked about the percentage of patients for whom they served as principal physician or the percentage of patients for whom only subspecialty care is provided. They were asked to identify the percentage of their professional patient-related activities devoted to family practice and to other specialties, and the year of graduation from medical school was also requested.

Complete responses were received from 59% of physicians surveyed. Response rates for internists and family practitioners were similar (56% for internists and 62% for family practitioners). Because of the anonymous nature of the survey, no follow-up was possible, and it was not possible to assess the representativeness of respondents compared with nonrespondents. To limit the analysis to primary care physicians, only internists who indicated that they serve as principal physician for at least 50% of their patients were included in analyses. Of the responding internists, 84% met this criterion as primary care physicians. Four family practitioners who spent most of their time in another specialty (emergency medicine or occupational medicine) were excluded from analyses. The results presented here are based on the responses of 156 internists and 99 family practitioners.

The number of HIV-infected patients seen per physician was tabulated from survey data as the sum of HIV-infected patients with or without AIDS seen by a physician in the past two years. Data analysis was performed with the Statistical Package for the Social Sciences personal computer software. Data were analyzed using Student's t test to determine differences between internists and family practitioners and one-way analysis of variance to determine differences between groups of physicians based on the number of HIV-infected patients treated in the past two years. For group comparisons for most analyses, physicians were divided into the following groups: 0 HIV-infected patients seen, 1 to 5 HIV-infected patients seen, 6 to 20 HIV-infected patients seen, and more than 20 HIV-infected patients seen. The α level for a significant difference was set at $P < .05$.

TABLE 1.—*Cases of Class IV Acquired Immunodeficiency Syndrome (AIDS) Reported by Washington State Physicians**

AIDS Cases Reported, No.	*Physicians, No.*
1	355
2-5	116
6-10	31
11-20	11
21-80	8

*Physicians from all medical specialties are represented in these data provided by the Washington State HIV/AIDS Epidemiology Unit for cases reported from January 1982 to June 1989.

Results

Based on data obtained from the Washington State HIV/AIDS Epidemiology Unit, 521 physicians in Washington in all medical specialties and all types of practice reported treating at least one patient with class IV AIDS between January 1982 and June 30, 1989. Of these 521 physicians, 471 reported treating fewer than 6 patients, 42 reported 6 to 20 patients, and 8 reported more than 20 patients (Table 1). No information was available concerning the inpatient versus outpatient status of these patients. Of the 1,382 cases reported, 633 patients (46%) were seen by physicians who had reported fewer than 5 class IV AIDS patients.

Responses to the questionnaire, which was mailed to randomly selected primary care physicians, showed that 26% of internists and 27% of family practitioners indicated that they had seen no HIV-infected patients, either with or without AIDS, in their practices in the past two years; 14% of internists and 19% of family practitioners reported seeing one HIV-infected patient in the past two years. Among internists, 43% had seen 1 to 5 HIV-infected patients, 19% had seen 6 to 20 HIV-infected patients, and 13% had seen more than 20 HIV-infected patients in the past two years. Among family practitioners, 55% had seen 1 to 5 HIV-infected patients, 12% had seen 6 to 20 HIV-infected patients, and 6% had seen more than 20 HIV-infected patients in the past two years. These differences in experience with HIV-infected patients between internists and family practitioners were not statisti-

TABLE 2.—*Distribution of Seropositive Patients Without the Acquired Immunodeficiency Syndrome (AIDS) Among Providers Who Have Seen Small Numbers of HIV-Infected Patients*

HIV-Infected Patients Seen by Physician, No.	*Internists Who Saw Only Seropositive Patients Without AIDS, No.* (%)*	*Family Practitioners Who Saw Only Seropositive Patients Without AIDS, No.* (%)*	*Total, Both Specialties, %*
1	9/21 (43)	8/19 (42)	43
2	5/16 (31)	4/16 (25)	28
3	1/15 (7)	1/13 (8)	7
4	1/8 (13)	0/4 (0)	8
5	0 (0)	0 (0)	0

HIV = human immunodeficiency virus

*The numbers represent number of physicians in this category versus those responding to the question.

TABLE 3.—*Human Immunodeficiency Virus (HIV)-Infected Patients Seen by Primary Care Internists and Family Practitioners by Geographic Location**

Specialty	Number (%)† of HIV-Infected Patients Seen				
	0	1-5	6-20	>20	Total
Internists					
Metropolitan area‡	18 (18)	40 (40)	24 (24)	17 (17)	99
Other areas	22 (41)	24 (44)	5 (9)	3 (6)	54
Family practitioners					
Metropolitan area‡	9 (16)	33 (58)	9 (16)	6 (11)	57
Other areas	18 (45)	20 (50)	2 (5)	0 (0)	40

*Reported experience of internists and family practitioners from the region's major metropolitan area (Seattle-Tacoma) and for other areas in Washington, Alaska, Montana, and Idaho. Data shown are the number and percentage of physicians who reported caring for the indicated number of HIV-infected patients in the past 2 years.

†Percentages total more than or less than 100% because of rounding.

‡Comparison between major metropolitan area and other areas was significant ($P < .005$).

cally significant. Ten internists (6%) and four family practitioners (4%) reported seeing at least 50 HIV-infected patients in the past two years.

Most internists and family practitioners who reported caring for patients with HIV infection had seen HIV-infected patients both with and without AIDS (68% of internists and 61% of family practitioners). Among physicians who reported seeing 1 to 5 HIV-infected patients with or without AIDS, the number of physicians who had seen only seropositive patients without AIDS declined as the total number of HIV-infected patients seen increased (Table 2). There were no statistically significant differences between internists and family practitioners in total number of HIV-infected patients with or without AIDS seen. In addition, within the groups that had experience with HIV-infected patients, there was only one statistically significant difference between family practitioners and internists in number of patients seen. Among physicians who saw 6 to 20 HIV-infected patients with or without AIDS in the past two years, internists reported seeing a mean of 4.4 (standard deviation [SD] 2.8) patients with AIDS, and family practitioners reported seeing a mean of 2.6 (SD 1) patients with AIDS ($P = .005$).

Analysis of the practice characteristics of the primary care providers indicated that most primary care providers who care for large numbers of HIV-infected patients are based in the major urban area in the Northwest (Table 3). However, 44% of primary care internists and 50% of family practitioners in communities outside the major regional metropolitan area (Seattle and Tacoma) had seen 1 to 5 HIV-infected patients (24 of 54 internists, 20 of 40 family practitioners). In all, 15% of primary care internists and 5% of family practitioners in communities outside the Seattle-Tacoma area had seen more than 5 HIV-infected patients. There were no statistically significant differences between internists and family practitioners in the number of HIV-infected patients seen by geographic location.

One provider characteristic, the duration of time elapsed since completing medical school, was significantly related to the number of HIV-infected patients in the physicians' practices (Table 4). Internists who reported no personal experience in caring for HIV-infected patients had completed medical school a mean of 26 years previously, and internists who reported caring for more than five patients with HIV in the past two years completed medical school a mean of 15 years previously. The comparison of number of years elapsed since medical school graduation was statistically significant between internists with no experience with HIV-infected patients and all other groups of internists with experience with HIV-infected patients ($P < .001$). Although there was no statistically significant difference among family practitioners in the number of years since graduating from medical school for different groups with experience treating HIV-infected patients, family practitioners who had seen no HIV-infected patients tended to have graduated earlier than family practitioners in the groups with some experience caring for HIV-infected patients.

Discussion

Although the data presented here do not contain information about whether surveyed physicians provided continuous care for HIV-infected patients seen in their practices, the results of this study indicate that the care of HIV-infected patients is not consistently concentrated in the hands of a small number of physicians. Rather, in some communities, the care of patients with HIV infection is diffused among many providers, and many physicians report seeing a small number of patients with HIV infection in their practices.

Initial data obtained to determine the number of physicians in all specialties in Washington who reported treating CDC class IV AIDS patients at least once indicate that 46% of the patients for whom class IV AIDS has been reported in the state of Washington are seen by physicians who have reported treating fewer than five patients with AIDS. Furthermore, based on data obtained from the Washington State HIV/AIDS Epidemiology Unit, 68% of all Washington physicians who have reported patients with AIDS reported only one patient. Stimulated by these findings, survey data were obtained from primary care internists and family practitioners throughout the Pacific Northwest. Of physicians who responded to the survey, 74% of internists and 73% of family practitioners indicated some experience in caring for patients with HIV infection. Among the four groups delineated to

TABLE 4.—*Years Elapsed Since Medical School Graduation Among Primary Care Physicians Caring for Patients With Human Immunodeficiency Virus (HIV) Infection**

HIV-Infected Patients, No.	Years Elapsed Since Graduation	
	Internists	Family Practitioners
0	26±10†	19±11
1-5	19±10	15±10
6-20	15±6	13±6
>20	15±9	13±7

*Mean number of years elapsed since medical school graduation ± standard deviation are given for internists and family practitioners caring for HIV-infected patients.

†Comparison between internists who had cared for no HIV-infected patients and groups of physicians who had cared for HIV-infected patients was significant ($P < .001$).

represent experience in caring for patients with HIV infection, the largest group consisted of physicians who reported seeing one to five HIV-infected patients in the past two years. Among the physicians who had seen only small numbers of HIV-infected patients, as the number of HIV-infected patients seen increased, the percentage of HIV-infected patients with AIDS also increased. These findings suggest that among physicians who have seen a small number of HIV-infected patients, most do not immediately refer these patients elsewhere for specialized care. Thus, it appears that many primary care physicians who have little experience with the illness are providing some care for HIV-infected patients.

Family practitioners and internists surveyed reported seeing similar numbers of HIV-infected patients with and without AIDS in their practices. The only significant difference between the two specialties was among physicians who had treated 6 to 20 HIV-infected patients. In this group, internists saw more patients with AIDS than family practitioners did.

The group of primary care internists who reported no experience in treating HIV-infected patients differed from those physicians with experience in at least one characteristic. Internists with no HIV-infected patients graduated from medical school earlier than physicians who reported experience in caring for HIV-infected patients. This finding suggests that age may be a factor related to the primary care physician's preparedness or willingness to treat HIV-infected patients and is consistent with findings in two previous studies in which a small number of years in practice was associated with increased AIDS-related competence.[16,18] In another recent study, physicians who completed training in the past five years were more likely to care for patients with AIDS.[4] Further research is needed to determine the effects of age and number of years in practice on the quality and degree of care given to HIV-infected patients.

Our study has limitations that may affect the generalizability of results. The anonymous nature of data collection prevented any follow-up or comparison between respondents and nonrespondents. Data obtained from the Washington State HIV/AIDS Epidemiology Unit are for the use of physicians from all specialties and therefore do not specifically address primary care. In addition, results obtained in this study represent data only for the Pacific Northwest. Although this region has a large male homosexual population, the population of HIV-infected intravenous drug users is relatively small.[19] Patterns of medical care may be different for intravenous drug users than for other at-risk populations. An additional limitation of this study, as discussed earlier, is the lack of data regarding the extent of primary care provided by physicians to HIV-infected patients and whether and at what point referral to other physicians occurred.

Despite these limitations, the findings from this study raise important questions about the care of HIV-infected and at-risk patients that should be addressed in future studies. The role of the primary care physician in relation to these patients encompasses a broad possible range of responsibility, including prevention education and counseling, risk screening, identification, early management, counseling, and treatment or assessment and referral for advanced care. Recent recommendations concerning the care of HIV-infected patients have included the creation of regional centers for the care and treatment of AIDS patients.[20] Our results suggest that many primary care physicians are seeing a small number of HIV-infected patients in addition to the concentration of many patients among few providers and that care is being provided for both early and advanced disease. Further work is needed to define the quality of care being provided by primary care physicians to HIV-infected patients and to assess primary prevention activities directed toward at-risk patients. Whether the care of advanced cases should be centralized in tertiary care centers may depend on the results of such studies. In addition, studies of the quality of care being given to HIV-infected and at-risk patients by primary care physicians and subspecialists may allow the identification of areas of deficiency in care to which future training and continuing medical education efforts should be directed.

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Articles

Evaluating Cancer Patients for Rehabilitation Potential

DAVID M. O'TOOLE, MD, *and* ALICE M. GOLDEN, RN, MSN, MBA, *Worcester, Massachusetts*

The Karnofsky performance scale is the most widely used method of quantifying cancer patients' ability to function. It has also been used to measure patients' function before and after treatment. Because identifying problems with function is the cornerstone of rehabilitating patients with cancer, we developed a table that relates the functional independence measure with the Karnofsky scale. This approach encourages oncologists to consider inpatient or outpatient rehabilitation services for a broader range of cancer patients. We assessed 70 cancer patients undergoing rehabilitation to identify similarities between the functional independence measure used at our facility and the Karnofsky scale. In activities we considered vital, only 14% of patients were independent with ambulation on admission and, at discharge, 80% were independent or supervised with ambulation. Toilet transfers and bowel and bladder continence improved by the time of discharge. Three months after they were discharged, 28 of the 37 patients had maintained their discharge function level or had improved. Of the original group, 19 had died.

(O'Toole DM, Golden AM: Evaluating cancer patients for rehabilitation potential. West J Med 1991 Oct; 155:384-387)

In the United States, cancer is diagnosed in one of three persons, and one of five of these will die of the disease. Advances in the medical treatment of cancer—largely in the form of chemotherapy—plus refinements in surgical techniques, total parenteral nutrition, and more precise methods of administering radiotherapy have contributed to the increased longevity of cancer patients. Many of these patients have residual impairments or pain that seriously affects their daily activities, quality of life, or potential for returning to school or work.

Lehmann evaluated hospital records of more than 800 patients with a diagnosis of cancer and attributed the failure of rehabilitation intervention to the lack of rehabilitation consultation. The primary barriers were that functional problems were not identified and appropriate referral was not made as physicians were unfamiliar with the concept of rehabilitation.[1]

When a diagnosis of cancer is made, an overwhelming number of issues will confront the patient, family, and care givers. Major problems are the unknown prognosis, the uncertain response to treatment, and direct or remote effects of the cancer itself. Will there be residua from radical surgical procedures, and what may be the toxic side effects of chemotherapy? How will these affect the patients' performance of daily activities, their jobs or education, or their family relationships? How about pain? How is the stress to patient and family managed?

Assessment Methods

Evaluating function is the cornerstone of cancer rehabilitation. It allows clinicians to identify physical and functional problems, set realistic goals, and prescribe rehabilitation.[2] Ideally, problems in functioning are identified in the acute care hospital so that a patient is introduced to the system and directed to rehabilitation early in the course of the disease. Further assessments may be made so that as the disease remits, stabilizes, or progresses, problems may be noted and programs prescribed (Figure 1).

Many functional assessment tools are available, but the Functional Independence Measure (FIM) (Figure 2) has been found to be effective with cancer patients. The FIM measures self-care, mobility, ambulation, bowel and bladder continence, communication, cognition, social interaction, and emotions. It does not measure pain, community activities, or availability of family support. It allows the identification of problems in basic "survival skills" and provides a method for measuring progress.

Because of the unstable nature of many patients with

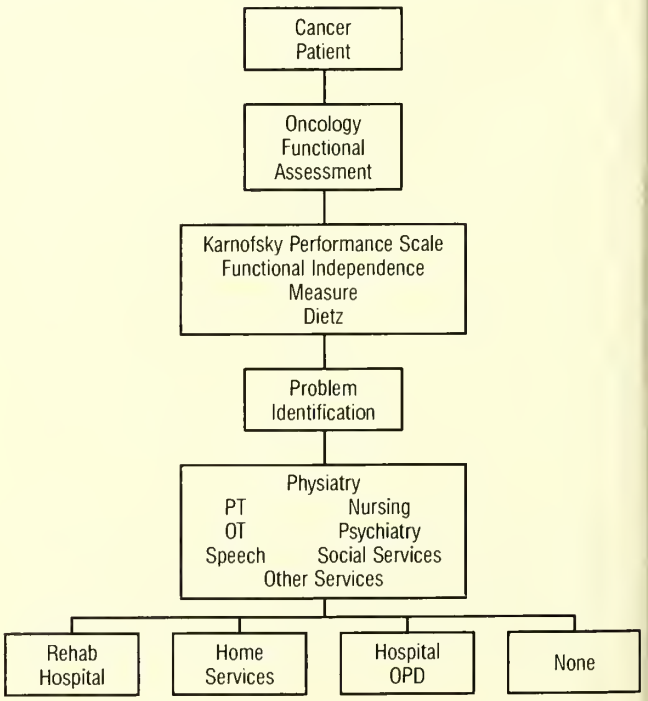

Figure 1.—Functional assessment for rehabilitation of cancer patients is shown in its various stages. OPD = outpatient department, OT = occupational therapy, PT = physical therapy

From the Departments of Rehabilitation Medicine (Dr O'Toole) and Quality Assurance Services (Ms Golden), Fairlawn Rehabilitation Hospital, Worcester, Massachusetts. Reprint requests to David M. O'Toole, MD, Fairlawn Rehabilitation Hospital, 189 May St, Worcester, MA 01602.

ABBREVIATIONS USED IN TEXT

FIM = Functional Independence Measure
KPS = Karnofsky Performance Scale

cancer, the prognosis is important in selecting patients. Dietz classified cancer patients into the categories of treatment: preventive, restorative, supportive, and palliative.[3]

The preventive (stage I) stage is the point at which preventing deconditioning and contractures is paramount. Appropriate management is in an acute care hospital or at the outpatient level. At the restorative stage (stage II), patients can be expected to return to their premorbid state without substantial disability. These patients may benefit from an orthosis or a prosthesis. The supportive stage (stage III) occurs when the disease has been controlled, even though there is known residual disease. Patients can be expected to return home and remain active even though functioning below the premorbid level. They often can return to work for an appreciable time. At the palliative stage (stage IV), an active rehabilitation program is not appropriate. This may be considered the hospice level.

Based on the clinical situation—the diagnosis, the effects of treatment, and complications, the functional assessment, and the Dietz oncology classification—realistic goals may be set. This system allows the primary care physician or oncologist to advise the patient and family of reasonable expectations and discharge planning needs. It is important not to foster false hopes.

Oncology rehabilitation differs little from rehabilitation of other disorders. The team must be flexible and have the ability to manage changes in a patient's status due to the disease or its treatment, however. Emotional considerations require mature, confident team members. Pain is more frequently a factor in cancer patients than in other diagnostic categories, and team members must be familiar with various modalities and techniques for pain management.

The basic treatment plans in physical therapy, occupational therapy, and speech therapy may have to be modified but are essentially the same as for other diagnoses. They include a strengthening and endurance program, neuromuscular reeducation, gait training, and a program to help the performance of activities of daily living. Patients in the restorative and the supportive stages will benefit from rehabilitation. Patients with hemiplegia; aphasia, dysarthria, and dysphagia from brain neoplasms; spinal cord compression resulting from primary or metastatic lesions; or severe deconditioning following surgical treatment or

Functional Independence Measure

Self-care
- Feeding
- Grooming
- Bathing
- Dressing upper body
- Dressing lower body
- Toileting

Sphincter Control
- Bladder
- Bowel

Transfers
- Bed/chair/wheelchair

Mobility
- Toilet
- Tub/shower

Locomotion
- Walk/wheelchair
- Stairs

Communication/Cognition
- Comprehension
- Expression
- Social interaction
- Problem solving
- Memory

Key
- 7 = Complete independence (unaided)
- 6 = Modified independence (device)
- 5 = Supervision
- 4 = Minimal assistance (completes 75% of activity)
- 3 = Moderate assistance (completes 50% of activity)
- 2 = Maximal assistance (completes 25% of activity)
- 1 = Total assistance required

Figure 2.—The Functional Independence Measure is a general assessment tool useful for determining whether cancer patients should be referred for rehabilitation.

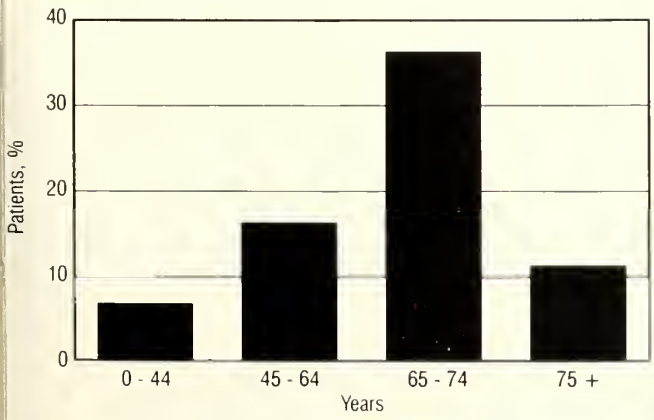

Figure 3.—The age distribution of the cancer patients studied is shown.

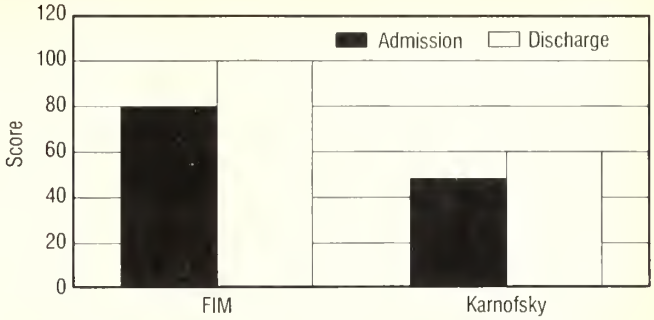

Figure 4.—The mean Functional Independence Measure (FIM) and Karnofsky Performance Status scores of the cancer patients studied are shown.

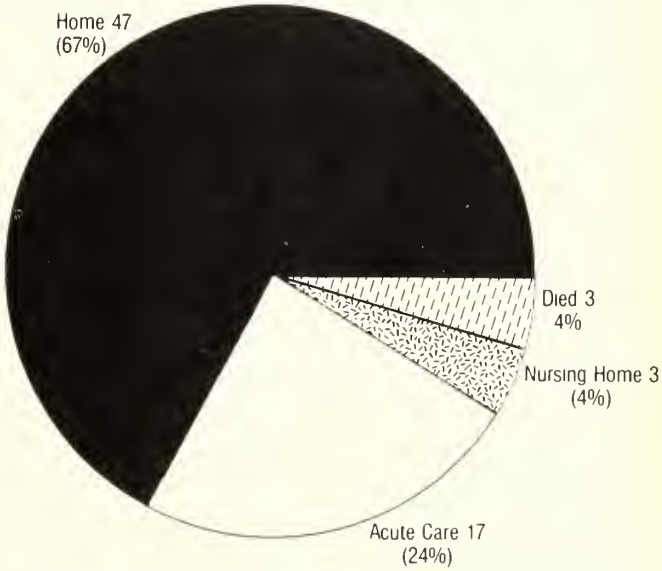

Figure 5.—Discharge destinations are shown for the cancer patients studied.

TABLE 1.—*Karnofsky Performance Scale Index**

General Category Description	*Specific Criteria*	*Index*
Able to carry on normal activity, no special care needed	Normal, no complaints, no evidence of disease	100
	Able to carry on normal activity, minor signs or symptoms of disease	90
	Normal activity with effort, some signs or symptoms of disease	80
Unable to work, able to live at home and care for most personal needs, varying amount of assistance needed	Cares for self, unable to carry on normal activity or to do work	70
	Requires occasional assistance from others, but able to care for most needs	60
	Requires considerable assistance from others and frequent medical care	50
Unable to care for self, requires institutional or hospital care, or equivalent disease may be rapidly progressing	Disabled, requires special care and assistance	40
	Severely disabled, stay in hospital indicated; death not imminent	30
	Very sick, stay in hospital necessary; active supportive treatment necessary	20
	Moribund	10
	Dead	0

*From Mor et al.[4]

chemotherapy all may have impairments that can be improved by rehabilitation.

Patient Selection

Fairlawn Rehabilitation Hospital is a free-standing, 80-bed, acute rehabilitation hospital. The Oncology Rehabilitation Program is staffed by a multidisciplinary team consisting of a physiatrist, a medical oncologist, rehabilitation nurses, physical therapists, occupational therapists, speech pathologists, a social worker, a pastor, and a neuropsychologist, with psychiatric and neurologic consultation available. Each patient admitted is evaluated by a preadmission nurse, and the patient's diagnosis, FIM, and Dietz stage are presented to the admission committee. Every effort is made to admit only patients in Dietz stages II and III who will have achievable goals. Pain management is an important goal.

A group of 70 consecutive patients admitted for oncology rehabilitation were retrospectively reviewed as part of our evaluation program and, based on FIM scores on admission, were given what we considered equivalent Karnofsky Performance Scale (KPS) index scores (Table 1).[4] In the sample, the range of FIM scores on admission was 37 to 117, equivalent to KPS scores of 30 to 70. These scores also were documented at discharge. A 90-day follow-up evaluation was done by telephone or by follow-up examination by the oncology physiatrist.

Results

Of the 70 patients in our program, 38 were women. The age distribution is shown in Figure 3. The average age was 71 years.

The average admission FIM score was 81, with a corresponding KPS score of 50. At discharge the average scores were FIM, 100 and KPS, 60 (Figure 4). At 90-day follow-up, 19 patients had died and 14 were lost to follow-up. Of the 37 patients remaining, 27 (73%) had maintained or improved their ability to function. The median length of hospital stay was 28 days, which compared favorably to that of stroke patients.

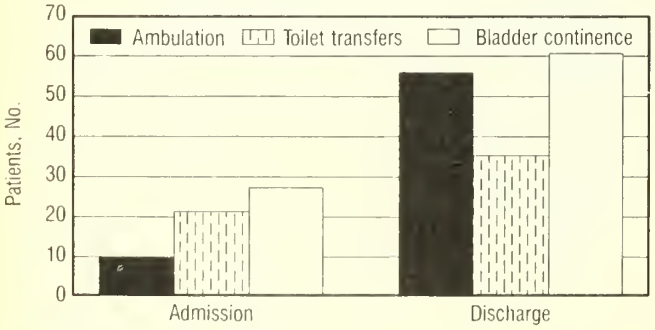

Figure 6.—Key functional activities are assessed before and after the hospital stay of cancer patients.

The destinations of patients discharged from oncology rehabilitation are shown in Figure 5. The number of patients discharged to home compares favorably with other diagnostic categories when age, diagnosis, and stability of the disease process are considered.

Initially, the perception was that only high-level patients were admitted to rehabilitation. Of the 70 patients admitted to our rehabilitation program, however, only 21 (30%) were independent in toilet transfers, 10 (14%) were independent with ambulation, and 26 (38%) had bladder continence. These are areas that are frequently overlooked when discharge from an acute care hospital is planned or that could require discharge to a nursing home.

At the time of discharge from the rehabilitation program, 35 (50%) were independent in toilet transfers, 56 (80%) were independent or supervised with ambulation, and 61 (87%) were bladder continent. Bowel programs were established so that 64 (91%) were continent (Figure 6).

Although 12% is an acceptable transfer rate for a free-standing rehabilitation hospital, 24% (17) of these patients required transfer back to an acute care hospital, reflecting the instability of many cancer patients. Of those requiring transfer, 6 had cancer of the lung, 3 had deep vein thrombosis, and the diagnoses for the rest ranged from dehydration because of intractable vomiting to gastrointestinal bleeding to pneumonia.

Admission FIM scores ranged from 65 to 101 (KPS 40 to 50), and, at admission, all of these patients were in the Dietz III category.

It is the policy of the rehabilitation program not to transfer cancer patients to an acute care hospital if death is imminent. Special relationships have been set up among the patient, the family, and the rehabilitation team, and, with the patient and

TABLE 2.—*Primary Diagnoses in 70 Patients in an Oncology Rehabilitation Program*

Primary Cancer Site	*Patients, No.*	*Primary Cancer Site*	*Patients, No.*
Brain	22	Endometrium	2
Lung	14	Ureter	2
Prostate	11	Thyroid	1
Breast	8	Esophagus	1
Colon	3	Larynx	1
Lymphoma	2	Unknown	1
Multiple myeloma	2		

TABLE 3.—*An Integrated Functional Assessment of Cancer Patients Using the Karnofsky Performance Scale (KPS) and the Functional Independence Measure (FIM)*

General Category*	Probable FIM Scores (KPS)	Useful Rehabilitation Treatment Modalities				
		Physiatry Consult	PT	OT	Speech	Nursing
A†	126 (100) No deficits	No	No	No	No	No
	126 (90) No deficits	Yes	Yes	Yes	Yes	Yes
	120-126 (80) May have minimal loss of function in mobility, continence, memory	Yes	Yes	Yes	Yes	Yes
B‡	115-120 (70) Increasing loss of function may require supervision	Yes	Yes	Yes	Yes	Yes
	90-115 (60) May require minimal assistance from others	Yes	Yes	Yes	Yes	Yes
	70-90 (50) Regularly requires moderate assistance with self-care	Yes	Yes	Yes	Yes	Yes
C§‖	60-70 (40) Needs maximum assistance for all activities of daily living	Yes	Yes	Yes	Yes	Yes
	40-60 (30)	Yes	Yes	Yes	Yes	Yes
	18-45 (20)	Yes	No	No	No	No
	18 (10)	No	No	No	No	No
	0 (0)	No	No	No	No	No

OT = occupational therapy, PT = physical therapy

*See Table 1 for a description of each category and the index scores.
†Corresponds to Dietz stage I, preventive.
‡Corresponds to Dietz stage II or III, restorative or supportive.
§Corresponds to Dietz stage III or IV, supportive or palliative.
‖One role of rehabilitation is to educate family members in providing safe and effective assistance with self-care activities.

family's permission, these patients remain in the rehabilitation program until they die. Of our 70 patients, 3 died. Cardiopulmonary failure occurred in two patients and severe bone marrow suppression with sepsis in the third. Cancer of the prostate with spinal cord compression was the diagnosis in two of the patients. Cancer of the bladder with bony metastases was the other diagnosis.

Diagnoses

The primary diagnoses are shown in Table 2. The average age of the group with brain tumors was 50, with a range from 22 years to 74 years. All were admitted from a university hospital neurosurgical service, with an average FIM score on admission of 71. Only 1 of the 22 patients was able to walk independently on admission. Of this group, 16 were discharged home, 4 were transferred to acute care hospitals, and 2 were discharged to nursing homes. At three months' follow-up, 10 had shown continued improvement in function, 3 had lost some function, and 9 were lost to follow-up.

Of patients with primary lung cancer, eight were discharged home and six required transfer to an acute care hospital. At 90-day follow-up, three had improved and two had lost function; nine were lost to follow-up.

Discussion

Even though this was not a controlled study, we are satisfied that there is a substantial population of patients with cancer who could benefit from rehabilitation. By using KPS scores, remediable problems can be identified and appropriate patients can be selected (Table 3).

The fact that 49 (70%) of our patients maintained or improved their functional status after 90 days is important. Cancer patients are capable of making notable gains in function and maintaining them. Considering the large percentage of patients who on admission were dependent with ambulation and toilet transfer and had bladder incontinence, the successful discharge-to-home rate was encouraging. Ambulation, transfers, and continence determine the success or failure of a home program. This may be overlooked when a patient is discharged from an acute care hospital. If oncologists, primary care physicians, and oncology nurses are aware of the use of the Karnofsky Performance Scale as an aid in selecting patients for rehabilitation consultation, quality of life will be improved for many cancer patients. There will be risks: The patient who appears to be doing well on initial assessment may have complications develop that interfere with rehabilitation and make it inappropriate. The team must be willing to accept this. With proper patient selection, results should be satisfactory. Rehabilitation evaluation must be done by a professional with experience with cancer rehabilitation.

Essentially, as used in oncology, the Karnofsky Performance Scale is a measure of time to death. When used as an adjunct in selecting appropriate patients for rehabilitation, it can be a measure of life.

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Conferences and Reviews

Molecular Genetics of Retinitis Pigmentosa

Moderotor
DEBORA B. FARBER, PhD
Discussonts
JOHN R. HECKENLIVELY, MD; ROBERT S. SPARKES, MD; *ond* J. BRONWYN BATEMAN, MD

This is an edited summary of an Interdepartmental Conference arranged by the Department of Medicine of the UCLA School of Medicine, Los Angeles. The Director of Conferences is Anthony T. Campagnoni, PhD, Professor of Biobehavioral Sciences.

Retinitis pigmentosa is a model for the study of genetic diseases. Its genetic heterogeneity is reflected in the different forms of inheritance (autosomal dominant, autosomal recessive, or X-linked) and, in a few families, in the presence of mutations in the visual pigment rhodopsin. Clinical and molecular genetic studies of these disorders are discussed. Animal models of retinal degeneration have been investigated for many years with the hope of gaining insight into the cause of photoreceptor cell death. Recently, the genes responsible for two of these animal disorders, the *rds* and *rd* mouse genes, have been isolated and characterized. The retinal degeneration of the *rd* mouse is presented in detail. The possible involvement of human analogues of these mouse genes in human retinal diseases is being investigated.

(Farber DB, Heckenlively JR, Sparkes RS, Bateman JB: Molecular genetics of retinitis pigmentosa. West J Med 1991 Oct; 155:388-399)

Debora B. Farber, PhD*: Recent advances in molecular genetics have made it possible to identify and isolate genes responsible for human diseases. One of these diseases, retinitis pigmentosa, will be the focus of our discussion. The methodologic approaches used in the study of this disease have been applied to the study of many other inherited disorders and, recently, for the isolation of the gene responsible for cystic fibrosis, an autosomal recessive disease. Some examples of gene defects identified using similar techniques are listed in Table 1.

Retinitis pigmentosa can be considered a model for the study of genetic disorders. It affects thousands of persons in the United States and many more all over the world. Patients and families affected with the disease and animals with inherited retinal degenerations similar to retinitis pigmentosa have been investigated for a number of years. Animal models have special advantages for the exploration of the aberrant mechanisms associated with the disease, such as the easier availability of tissues of defined age, sex, and genetic background.

What is the primary lesion in retinitis pigmentosa that causes the retinal photoreceptor cells to die and leads to eventual blindness? If the origin of the disease can be elucidated, it may be possible to design treatments that will arrest or cure it. Unfortunately, retinitis pigmentosa is not one disease but the name given to an umbrella of disorders that have blindness as a common end. It has therefore been necessary to classify the different types of retinitis pigmentosa and its related syndromes to group patients and families. Only in this way can the genetic background be appropriately correlated with biochemical, cell and molecular biologic, and physiologic findings. Classification systems based only on clinical features, however, may not always correlate with the genetic defects.

Our understanding of the mechanisms that may be abnormal in specific types of retinitis pigmentosa has been substantially advanced during the past five years, due largely to the application of the techniques of molecular biology. Indeed, during 1989, a gene involved in the disease of a family with autosomal dominant retinitis pigmentosa was localized to the long arm of human chromosome 3,[1] and the genes responsible for the retinal degeneration of two different animal models, the *rds* mouse[2] and the *rd* mouse,[3] were isolated and characterized.

The heterogeneity of retinitis pigmentosa and the classification of its different types are discussed first. We then describe the general approaches that have been used to study these diseases using specific examples. We also summarize the results of our work on the *rd* mouse, including the isolation and characterization of the gene responsible for the degeneration of the *rd* photoreceptor cells, and show that biochemical abnormalities similar to those in the *rd* mouse were present in a patient with dominant retinitis pigmentosa whom we have studied.

TABLE 1.—*Genetic Disorders for Which the Condidate Gene Approoch Hos Proved or Is Proving Useful in Identifying (Isoloting) the Responsible Gene(s)*

Atherosclerosis	Duchenne muscular dystrophy
Colon cancer	Alcoholism
Retinoblastoma	Schizophrenia
Neurofibromatosis	Diabetes mellitus
Cystic fibrosis	Spinocerebellar atrophy

*The Jules Stein Eye Institute and the Department of Ophthalmology, UCLA School of Medicine.

This study was supported by National Institutes of Health grants EY02651 and EY08285 (Dr Farber), EY07758 (Dr Heckenlively), and EY08082 (Dr Bateman); Research to Prevent Blindness, Inc, William and Mary Greve International Scholar Award (Dr Bateman); The National Retinitis Pigmentosa Foundation (Dr Farber); and The George Gund/National Retinitis Pigmentosa Foundation Grant (Drs Sparkes, Bateman, and Farber). Dr Farber is a recipient of a Research to Prevent Blindness Senior Scientific Investigators Award.

Reprint requests to Debora B. Farber, PhD, Jules Stein Eye Institute, UCLA School of Medicine, Los Angeles, CA 90024-1771.

ABBREVIATIONS USED IN TEXT

ATP = adenosine triphosphate
cDNA = complementary DNA
cGMP = cyclic guanosine monophosphate
mRNA = messenger RNA
OAT = ornithine aminotransferase
RFLP = restriction-fragment-length polymorphism

Definition and Clinical Findings in Retinitis Pigmentosa

JOHN R. HECKENLIVELY, MD*: Retinitis pigmentosa is the name given to a set of diseases that have in common a progressive retinal degeneration characterized by progressive visual field loss, a pigmentary retinopathy, and, at some point in the disease, night blindness.[4] This broad definition encompasses a large number of ocular-only forms and secondary types in which the pigmentary retinopathy is part of a syndrome or a systemic disease. Most forms of retinitis pigmentosa begin in adult life, but less commonly it may be congenital or manifest itself in childhood.[5] The term "retinitis" is a misnomer because there is little evidence that inflammatory processes are involved in any important way in these diseases.

The estimated incidence of retinitis pigmentosa (all types) in the United States is 1 in 3,500, and the carrier state may be as frequent as 1 in 80 persons.[6] The most common mendelian inheritance pattern in the United States is autosomal recessive at 31%; autosomal dominant represents 17%, and X-linked recessive is the least common at 10% (Table 2).[7-10] Many patients with the disease (42%) have no family history and are often said to have "simplex" inheritance. Retinitis pigmentosa is found in all races; the distribution in racial subgroups closely follows that found for the normal population (Table 3).[11,12]

X-Linked recessive inheritance is the least common of the retinitis pigmentosa inheritance types, but it often is the best remembered. Many male patients with the disease, without having a family pedigree taken, are told inappropriately by their physicians that they inherited it from their mother. This may cause feelings of guilt in the mother and resentment toward the mother by the son. Similarly, many of these patients are told not to have children as "they will inherit the disease." In fact, only patients with the autosomal dominant form—less than 20% of affected patients—are at immediate risk of passing the disease to their children.

The diagnosis is typically made by finding that a patient has a visual field loss in a pattern characteristic of retinitis pigmentosa and seeing a pigmentary retinopathy on fundus examination. An electroretinogram is an important confirmatory test, and the results will be abnormal to nonrecordable by standard single-flash techniques.[8]

*The Jules Stein Eye Institute and the Department of Ophthalmology, UCLA School of Medicine.

TABLE 3.—*Retinitis Pigmentosa (RP) Population: Distribution by Race*

Race or Ethnicity	*UCLA RP Registry,** %	*Normal California,†* %	*Normal United States,†* %
White	81	76	83
African American	4	8	12
Hispanic‡	9	19	6.5
Asian	5	5	1.5
American Indian	1	1	0.5

*Data on 500 patients.
†From Statistical Abstracts of the United States 1984[11]; reproduced by permission of the US Department of Commerce.
‡Includes all persons of Spanish origin and overlaps with other categories (from Heckenlively et al[12]).

At least 14 forms of ocular-only retinitis pigmentosa can be identified by clinical criteria of inheritance pattern, changes on the electroretinogram, the measurement of rod function, and retinal appearance (Table 4).[5,13-26] Why are there so many types of retinitis pigmentosa? Most of these disorders arise from dysfunction or maldevelopment of the retinal pigment epithelium or the photoreceptors (Figure 1).[27(p43)] Multiple pathways are known to be essential; if they are disrupted, the photoreceptors will degenerate. Each of these pathways is presumably under the control of separate genes.

Several systemic syndromes include a progressive pigmentary retinopathy. The most common, the Usher syndrome, is characterized by retinitis pigmentosa and congenital hearing loss that may be complete or partial. Clinical evidence suggests that these two forms of the Usher syndrome are caused by different genes. Type II was recently linked to the long arm of chromosome 1.[28] The Usher syndrome constitutes about 10% of patients with retinitis pigmentosa seen at UCLA. Surveys for this disease at schools for the deaf often find a 3% to 6% prevalence in the students.[25]

The next most common retinitis pigmentosa syndrome (slightly less than a 1% prevalence in the UCLA RP Registry) is the Bardet-Biedl syndrome, characterized by polydactyly, obesity, short stature, mild mental retardation, and hypogonadism. In this syndrome, the retinal degeneration usually includes a macular degeneration.[29]

Most of the more common types of retinitis pigmentosa tend to have a similar appearance of the fundus: diffuse retinal atrophy and retinal vessel attenuation, with either release of pigment or migration of retinal pigment epithelial cells that aggregate on retinal vessels, particularly at bifurcations. This gives a characteristic bone spicule-like pigmentary pattern (Figure 2).[30] Degeneration typically starts in the equatorial retina and can be measured on the visual field test. The affected retina in this area becomes less sensitive to stimula-

TABLE 2.—*Distribution of Retinitis Pigmentosa by Mendelian Inheritance*

Study	*Population*	*Patients, No.*	*Simplex,* %	*Autosomal Recessive,* %	*Autosomal Dominant,* %	*X-Linked,* %
Boughman and co-workers, 1980[7]*	United States*	670	15*	69	10	6
Heckenlively, 1987[8]	California	609	42	31	17	10
Boughman and Fishman, 1981[9]	Illinois	300	50	16	22	9
Jay, 1982[10]	England	426	42	16	24	18

*Represents proportion of cases not accounted for by probability alone.

TABLE 4.—*Ocular-only Types of Retinitis Pigmentosa (RP) Due to Single Gene Site Abnormalities and Identified Clinically or Genetically*

Type	*Source*
Autosomal Dominant	
Rhodopsin mutations (chromosome 3)	Dryja et al, 1991[13]
Chromosome 8 RP1 gene	Blanton et al, in press[14]
Infantile onset (rare)	Heckenlively, 1988[15]
Irish family chromosome 3 (not rhodopsin)	McWilliams et al, 1989[16]
Others (rod-cone and cone-rod degenerations)	Heckenlively, 1987[17]
Autosomal Recessive	
Type I (rod-cone)	Heckenlively, 1987[17]
Type II (cone-rod)	Heckenlively, 1987[17]
Preserved para-arteriolar retinal pigment epithelial RP	Heckenlively, 1981[18]
Leber's amaurosis congenita (typical)	Foxman et al, 1985[5]
Congenital RP with macular colobomata	Heckenlively et al, 1988[19]
Juvenile RP	Foxman et al[5]
Retinitis punctata albescens	Ellis and Heckenlively, 1983[20]
Goldmann-Favre disease	Favre, 1958[21]
X-Linked Recessive	
Choroideremia (Xq21)	Cremers et al, 1989[22]
Retinitis pigmentosa*	Bird, 1975[24]
Common RP Syndromes (autosomal recessive)	
Usher type I (congenital profound deafness and RP)	Fishman et al, 1983[25]
Usher type II (congenital partial deafness and RP)	Fishman et al, 1983[25]
Bardet-Biedl (polydactyly, obesity, mild mental retardation, hypogonadism, pigmentary retinopathy)	Schachat and Maumenee, 1982[26]

*Two gene sites have been identified on the X chromosome for retinitis pigmentosa (from Musarella et al, 1988[23]).

tion, and often a "ring scotoma" will be found where there is intact functioning central and peripheral retina, but the mid-peripheral retina does not "see" the test target, and a donut of vision loss can be mapped (Figure 3).[31] At this stage of the disease, patients begin to bump into objects in their path because they do not see them.

Many of the patients with retinitis pigmentosa have a typical pattern of visual field loss; it starts in the equatorial region, then involves the anterior retina and may leave a peripheral ring with a central island of intact vision, similar to that shown in Figure 3. With further progression, the peripheral ring and central area diminish in size, and eventually in some patients the central vision desaturates and fails.[31] Some patients will maintain good central vision into advanced states of the disease, even though they will have a severe disability because they cannot see anything outside the central tubular field.

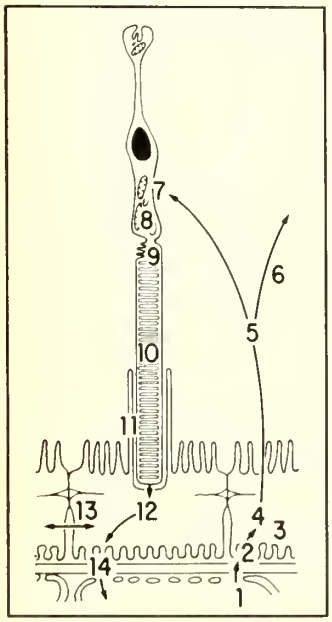

Figure 1.—A diagram is shown of mechanisms that may be involved in the degeneration of photoreceptor cells; the figure shows interaction of photoreceptor and retinal pigment epithelial (RPE) cells: **1**, uptake or transport defect; **2**, abnormal membrane receptor sites in RPE; **3**, intracellular RPE metabolic defects; **4**, transepithelial transport defect; **5**, RPE to photoreceptor donor defect; **6**, RPE to other retinal cell defects (such as Mueller cells); **7**, abnormal sites in photoreceptor cell; **8**, micrometabolism malfunctions; **9**, faulty membranogenesis; **10**, inability to stabilize membranes; **11**, malfunction in phagocytosis; **12**, malfunction in lysis; **13**, defective RPE lateral transport and communication; **14**, inability to void lytic products (from Heckenlively[27]; reproduced with permission from JB Lippincott Co).

Natural History of Retinitis Pigmentosa

Patients with retinitis pigmentosa have been reported to lose on the average about 4.6% of remaining visual field each year.[32] Studies at UCLA looking at visual field loss of this disease found a mean deterioration of 7.7% per year (mea-

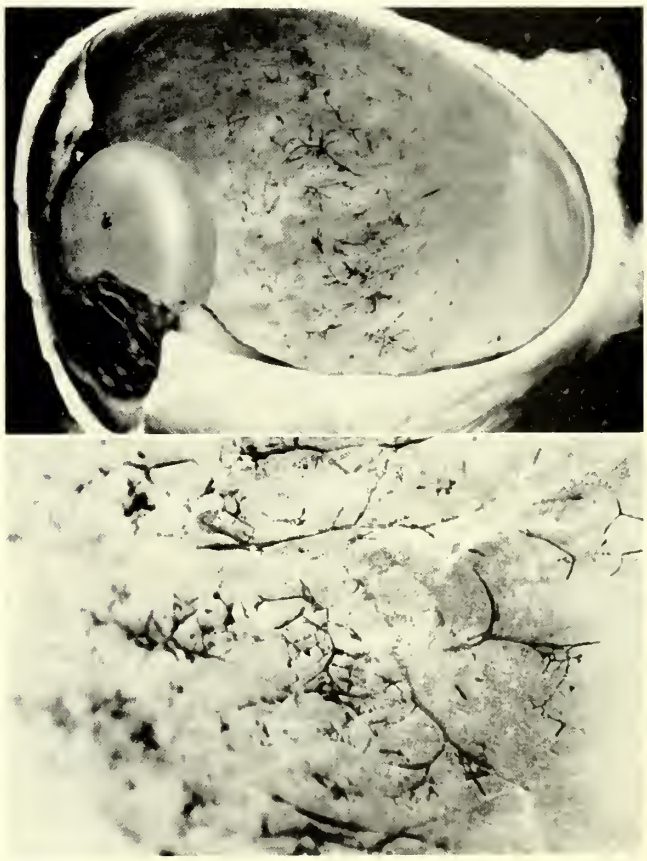

Figure 2.—**Top,** A gross specimen of eye taken at autopsy from a man with advanced retinitis pigmentosa shows distribution of pigmentation in equatorial regions. **Bottom,** A magnified view of the retina shows pigment clumping on retinal vessels and in the retina. Full report available (from Meyer et al[30]).

suring visual field loss over time). This rate dropped to a mean of 3.5% in a group of 39 study patients with retinitis pigmentosa placed on a regimen of vitamin E and β-carotene and observed for an average of eight years.[33] Statistically significant levels of improvement were not reached due in part to the large variance in the visual field measurements.[34,35] The use of antioxidants has been suggested to be of benefit in several ocular conditions.[36]

Retinitis pigmentosa does not result in sudden blindness. The disease typically progresses slowly over three to five decades after its usual first manifestation from age 20 to 30 years. Most patients do not go blind from the disease therefore, but many will have a severe disability in more advanced stages and may be legally blind (visual field 10 degrees or less with a 3-mm white target).

In almost half of patients with retinitis pigmentosa, posterior subcapsular cataracts also develop, some of which will cause enough visual loss to necessitate surgical correction. After cataract operations, patients do well, and there is no evidence that retinal degeneration is exacerbated, but there is an average delay of two months in achieving best visual acuity when compared with regular patients with cataracts.[37]

The use of molecular biologic techniques promises to be of great help to clinicians in sorting out the many forms of retinitis pigmentosa. There is also the potential of more rational treatment and more accurate genetic counseling. Linkage studies have already shown at least two gene sites on the X chromosome, possibly with different forms of the disease.[23] In an important recent study, 17 of 148 (12%) patients from different pedigrees with autosomal dominant retinitis pigmentosa were found to have a base-pair substitution in the rhodopsin gene.[1]

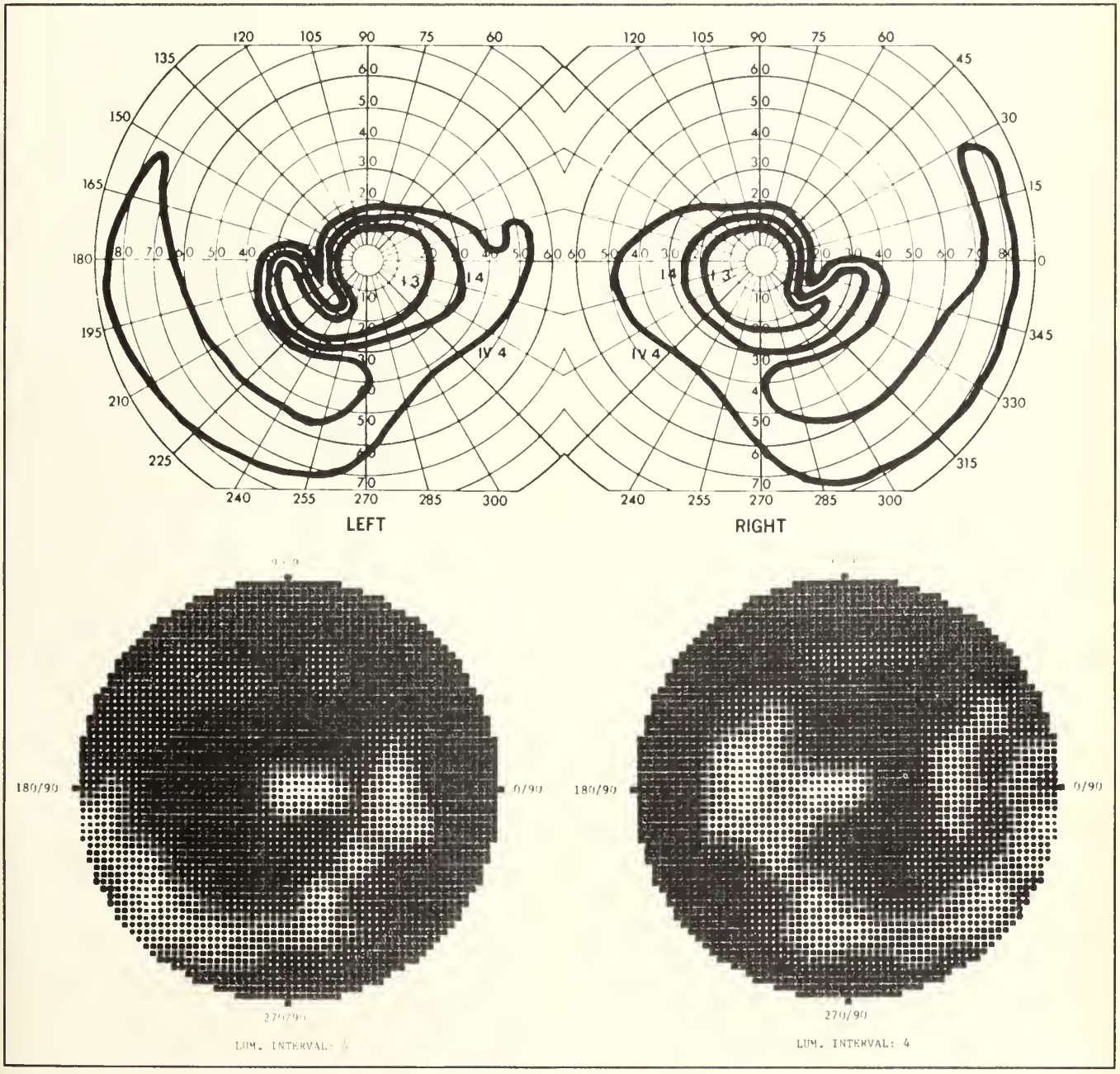

Figure 3.—Goldmann visual field **(top)** and octopus visual field **(bottom left and right)** from a 33-year-old man with autosomal dominant rod-cone degeneration show superior visual field depression and midperipheral ring scotoma formation (from Heckenlively[31]; reproduced with permission from JB Lippincott Co).

Genetic Approaches to Retinitis Pigmentosa

ROBERT S. SPARKES, MD*: Family studies have indicated that many types of retinitis pigmentosa have a genetic basis. This in turn suggests the possibility of considerable genetic heterogeneity as the basis for retinitis pigmentosa. It is important to identify the genes responsible for these disorders:

- Our understanding of their normal and abnormal functions would be improved.
- Rational forms of treatment might be developed at the physiologic or biochemical level.
- Gene therapy may become available sometime in the distant future.
- This information can be used to improve genetic counseling, probably at the prenatal and postnatal levels, by facilitating early detection of persons at risk. This may also lead to preventive measures once the basis of the disorder is understood in a given person or family.

At present, there are two ways to identify the genes responsible for genetic disorders. The first is through the use of general genetic linkage analysis, which focuses on finding the approximate position in the genome of the responsible gene. From this starting point, various techniques can be used to sequence into the responsible gene, as has been done recently for cystic fibrosis.[38] The second genetic approach is the use of candidate genes. For example, genes whose function might conceivably be related to the development of retinitis pigmentosa are identified and mapped to chromosomal regions where perhaps general linkage has suggested the location of a responsible gene.

The mapping of genes can be carried out at different levels. The first is by assigning a gene to a chromosome through the use of general linkage analysis, or the use of interspecific somatic cell hybrids, or through the use of in situ hybridization. Finer mapping can then be done through the use of studies of DNA at more restrictive levels. Finally, the specific point mutation can be identified by DNA sequencing.

For general genetic linkage, large families with the affected trait should be identified to limit the possible confounding aspects of genetic heterogeneity when different families are studied. Such families are then studied through the use of genetic markers to try to determine linkage between the disease locus and one of a number of laboratory markers. For many years, only a few phenotypic polymorphic markers were available, such as the erythrocyte antigens, erythrocyte isoenzymes, and serum protein variants. Now these markers can be extensively complemented and supplemented through the study of DNA variations, especially through the use of restriction-fragment-length polymorphisms (RFLP). In this sensitive technique, variations in DNA sequence can be identified through the use of restriction enzymes that cut the DNA at specific sites, yielding fragments of characteristic length.

Our own work has largely focused on the use of candidate genes identified according to the following criteria: First, the candidate gene must be expressed in the affected tissue. Second, the known biologic or biochemical function of the gene should allow a rational postulate that it be related to the disease of interest. Third, the relevant map position indicates that the gene could be involved in the disease. (This can be further evaluated by showing linkage cosegregation of the disease gene with the test gene in families.) Finally, molecular changes may be able to be shown in the gene by several techniques.

Animal homologies as discussed later may also often give clues as to which genes may be candidate genes. For several reasons, the study of candidate genes seems appropriate at this time. Several tissue-specific complementary DNA (cDNA) libraries are available. Easily sampled tissues, such as blood cells, can be obtained for the analysis of tissue-specific diseases, even though the gene of interest may not lead to blood disease but be expressed in some other tissues, such as the retina. Several mapping techniques are available to assign the gene to a specific chromosome and chromosomal region. Several technologies have been developed to study DNA variation that can be useful for genetic linkage analysis. Compared with general linkage analysis, the candidate gene approach has some advantages. In the candidate gene approach, cDNAs of genes, mutations of which are thought likely to be responsible for disease, are used. These cDNAs have often been well characterized, which makes it relatively easy to look for alterations in relation to a disease. This has been recently nicely shown in the mutation in rhodopsin in one form of retinitis pigmentosa, as discussed later in this article.[1]

Several years ago, studies on animal models of retinal degeneration (see last section of this article) identified an abnormality in the activity of cyclic guanosine monophosphate (cGMP)-phosphodiesterase, a key enzyme in the transduction pathway for transmitting a light signal to the brain. This abnormality may also be present in retinitis pigmentosa. Because a defect in cGMP-phosphodiesterase activity could result from an abnormality in the enzyme itself or in any of the members of the complex system of proteins that modulate its activity, several possible candidate genes could be involved in retinitis pigmentosa. Some of these include the

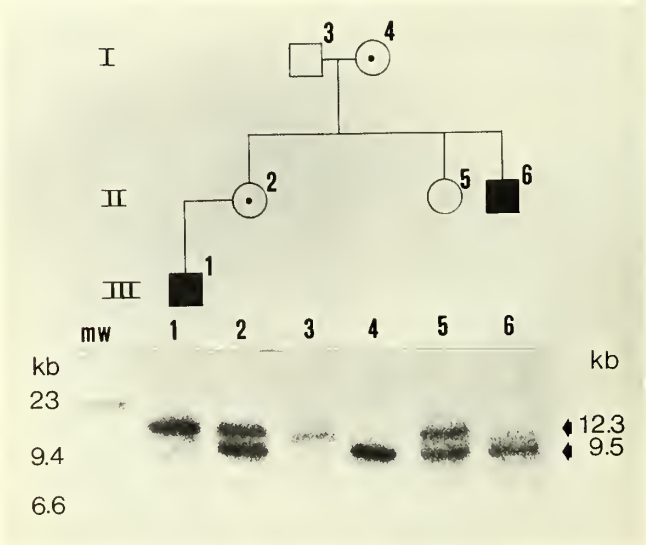

Figure 4.—A pedigree and autoradiograph are given. In a *Taq* I digest of human genomic DNA, the probe L1.28 detects two alleles of fragment sizes 12.3 kb and 9.5 kb. Black symbols represent men with Norrie's disease; obligate carriers are identified by circles with a dot. The carrier state is undeterminable in patient 5, and a recombination event betwen the DXS7 locus and the Norrie's disease locus has occurred in patient 2. The lane marked "mw" shows molecular weight markers using *Hin*dIII-digested λ (from Ngo et al[55]; reproduced with permission from *Clinical Genetics*).

*Division of Genetics, Department of Medicine, UCLA School of Medicine.

TABLE 5.—*Lod Scores Between the Norrie's Disease and the DXS7 Loci**

Family (Locus)‡	Lod Scores at Recombination Fractions (θ)†						
	0.00	0.01	0.05	0.10	0.20	0.30	0.40
Bleeker-Wagemakers et al (Ja)[51]	0.81	0,80	0.74	0.67	0.52	0.35	0.17
Bleeker-Wagemakers et al (P 2248)[51]	2.18	1.24	1.98	1.77	1.35	0.90	0.45
Bleeker-Wagemakers et al (P 2785)[51]	0.90	0.89	0.84	0.77	0.61	0.44	0.24
De la Chapelle et al[52]	2.41	2.37	2.21	2.00	1.56	1.09	0.57
Kivlin et al[53]	1.61	1.58	1.46	1.29	0.94	0.56	0.21
Hill et al[54]	1.41	1.38	1.28	1.15	0.86	0.54	0.24
Total	9.32	9.16	8.51	7.65	5.84	3.88	1.87
Present family	−∞	−1.70	−1.00	−0.70	−0.40	−0.22	−0.10
Total (present study)	−∞	7.46	7.51	6.95	5.44	3.66	1.77

*Not shown are 3 families reported by Bleeker-Wagemakers et al[51] and identified as P, P 9500, and "unpublished"; all are uninformative for the marker and give lod scores of 0.00 at all recombination fractions.

†The recombination fractions for women and men were equal.

‡Lod scores from the 6 families are recalculated on the basis of their published pedigrees (from Ngo et al[55]).

different subunits of G proteins (rod and cone transducins), rhodopsin, S antigen, the subunits of rod and cone cGMP-phosphodiesterases, and even the interphotoreceptor retinol-binding protein.

As noted, an abnormality of rhodopsin occurs in a form of autosomal dominant retinitis pigmentosa, a point of special interest in the candidate gene approach. The gene for human rhodopsin has been mapped to the long arm of chromosome 3.[39,40] The gene for autosomal dominant retinitis pigmentosa has been linked in a large Irish family to an anonymous probe (C17) that is located on the long arm of chromosome 3.[16] Dryja and colleagues picked up on this finding and examined the rhodopsin gene directly in other families with autosomal dominant retinitis pigmentosa.[1] They found that about 10% of the families with this type of condition had a mutation within codon 23 (CCC to CAC) of the first exon. They were then able to screen relatively quickly using specific oligonucleotide probes to identify persons who may or may not have this change. They found this change in 17 of 148 unrelated patients but not in any of 102 unaffected persons. This strongly supports the postulate that this point mutation is responsible for the retinitis pigmentosa in the families studied.

Thus, through the use of genetic techniques, especially the candidate gene approach, a gene responsible for a disease can sometimes be quickly identified, and the genetic basis for a disease can begin to be understood.

Hereditary Retinal Disease—Molecular Studies on Human Families

J. Bronwyn Bateman, MD*: The candidate gene approach has been used in our laboratory to study two retinal diseases that have a genetic basis: Norrie's disease and retinitis pigmentosa. Norrie's disease is an X-linked recessive disorder characterized by retinal detachment early in life.[41-46] As the retina is an extension of the brain and its function is to transform light energy to nervous impulses, both mechanical and biochemical abnormalities can cause profound loss of vision. The retina is nourished from the layer of pigment epithelial cells with which it is in close contact; if it becomes detached from this layer, atrophy, disorganization, and loss of function ensue. Complete blindness eventually occurs. In Norrie's disease, the retina detaches from the retinal pigment epithelium, and this causes profound and usually complete loss of vision. Additional features include variable mental retardation and hearing loss.

The gene for Norrie's disease was localized to the X chromosome by the characteristic inheritance pattern. As DNA probes for the X chromosome became available, close linkage between an RFLP identified by the DNA probe L1.28 (DXS7) and the disease was described in the mid-1980s. The L1.28 probe is an "anonymous" probe of unknown purpose that had been assigned to the region p11.3-p11.4 of the X chromosome[47,48]; therefore, the gene for Norrie's disease was assigned to the same area. The cumulative lod score, which reflects the statistical likelihood of linkage (or proximity) between the two genes, was 9.32 at a recombination fraction of 0.00 by 1987.[49-54] A lod score of this magnitude indicates that many meioses (informative matings) had been studied without a single recombinational event between the L1.28 probe and Norrie's disease loci. In other words, the genes for L1.28 and Norrie's disease had to be in close proximity on the X chromosome, or, alternatively, the Norrie's disease gene was within the L1.28 sequence.

We studied a family affected with X-linked recessive Norrie's disease and identified the first recombinational event between the disease locus and the DXS7 locus identified by the probe L1.28 (Figure 4).[55] We recalculated the lod score for the previously published cases and, with the addition of the UCLA family, changed the maximum lod score to 7.58 at a recombination frequency of 0.038 ± 0.036 (Table 5).[51-55] This finding indicated that the L1.28 probe is useful but may not be completely reliable for prenatal diagnosis and that the gene for Norrie's disease is not within the DNA sequence identified by the L1.28 probe.

We then looked for an alternative candidate gene in an effort to identify other probes for prenatal or perinatal diagnosis. Ornithine aminotransferase (OAT; L-ornithine:2-oxo-acid aminotransferase, EC 2.6.1.13) is a mitochondrial matrix enzyme catalyzing the major catabolic pathway of ornithine in human tissues. It has been mapped to the same region of the X chromosome as L1.28. A cDNA clone for the messenger RNA (mRNA) encoding human OAT (pHOAT) has been isolated and characterized.[56] Our group used somatic cell hybrids and in situ hybridization to map OAT and OAT-like gene sequences to two human chromosomes in regions 10q26 and Xp11.2[57] and used somatic cell hybrids to localize the genes to regions 10q23 and Xp11-Xp21.[58] This

*The Jules Stein Eye Institute and the Department of Ophthalmology, UCLA School of Medicine.

enzyme is present in many mammalian tissues,[59] including the retina, retinal pigment epithelium, and ciliary body of the eye.[60] An absence or severe deficiency of OAT is thought to be the primary defect in patients with gyrate atrophy,[61-64] an autosomal recessive ocular disease marked by myopia, cataracts, and a severe progressive degeneration of the choroid and retina.[61,65]

The X chromosome-associated OAT-like gene sequences (Xp11.2)[57] share the same general chromosomal regional assignment as the L1.28 probe (Xp11.2-Xp11.3). Although abnormalities of OAT activity (chromosome 10) had not been reported in patients with Norrie's disease, the proximity of OAT-like gene sequences to the L1.28 probe on the X chromosome made it a good candidate gene.

In this study, we used a human OAT cDNA to investigate the UCLA family with Norrie's disease that had shown the recombinational event. When genomic DNA from this family was digested with the *Pvu* II restriction endonuclease, a complex pattern of at least 14 bands was found. Only one of these bands (11.2 kb) is specifically localized to chromosome 10; the remaining identifiable 12 bands map to the X chromosome. We detected an RFLP of 4.2 kb. The 4.2-kb fragment was absent in the affected men and cosegregated with the disease locus (Figure 5; Table 6)[66]; we calculated a lod score of 0.602, at $\theta = 0.000$ (Table 7). No deletion could

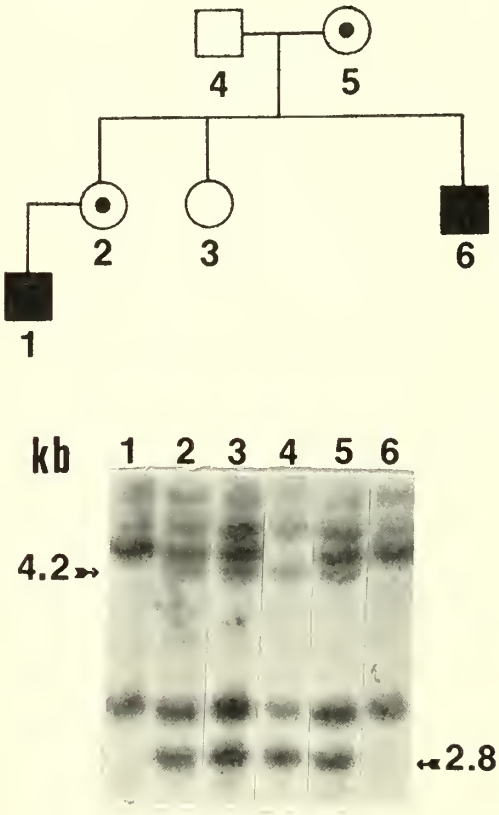

Figure 5.—A pedigree and Southern blot hybridization pattern show the distribution of the 4.2-kb restriction-fragment-length polymorphism (RFLP) from a 6-member family affected with Norrie's disease. The number of each lane corresponds to the number assigned to the persons in the pedigree. Genomic DNA was digested with *Pvu* II endonuclease and hybridized to ornithine aminotranferase (OAT) complementary DNA probe. A circle with a dot indicates the carrier state as determined by the L1.28 probe, and the arrow marks the RFLP. The status of person 3 is indeterminable using the L1.28 probe and is heterozygous based on the 4.2-kb band identified by the OAT cDNA probe (from Ngo et al[66]; reproduced with permission from *Genomics*).

TABLE 6.—*Mendelian Inheritance of the 4.2-kb Fragment: Copy Number Determined by Laser Densitometry**

Status	*Sex*	*Density of 11.2-kb Band (area in AU/mm)*	*Density of 4.2-kb Band (area in AU/mm)*	*Ratio of Density*	*Copy Number (Person)†*
Carrier	F	6.79	0.21	0.031	1(#2)
Carrier	F	6.04	0.34	0.056	1(#5)
Normal	M	1.27	0.06	0.049	1(#4)
Normal	F	2.22	0.22	0.099	2
Unknown ...	F	6.53	0.29	0.045	1(#3)

AU = absorption unit

*Genomic DNA from each of these persons was digested with *Pvu* II endonuclease and subjected to agarose gel electrophoresis to separate the fragments. The bands that contained ornithine aminotransferase (OAT) or OAT-related sequences were detected by autoradiography using a human OAT complementary DNA labeled with phosphorus 32. Using the LKB 2400 GelScan XL densitometer, we measured the density of the OAT hybridizable bands on the autoradiogram, which were reported as area (AU/mm). The OAT band representing the functional OAT gene on chromosome 10 (11.2-kb fragment) was used as an internal standard. The ratio of the 4.2- and the 11.2-kb band was determined to calculate the copy number of the 4.2-kb fragment. The normal female used in this study is from a family without Norrie's disease. It is assumed that the normal persons tested are homozygous for the allele represented by the 11.2-kb fragment. The resulting inference regarding the number of alleles at the OAT-related locus is confirmed by the distribution of the marker locus phenotype in this family (from Ngo et al[66]).

†The number in parentheses corresponds to the persons in the pedigree (see Figure 5).

be detected by chromosomal analysis of Southern blots with other enzymes. These results suggested that one of the OAT-related sequences on the X chromosome could be in close proximity to the Norrie's disease locus and represented the first report that the OAT cDNA may be useful for identifying the carrier state or for prenatal diagnosis, or both.[66]

Because the lod score obtained with the human OAT probe was not statistically significant to establish linkage, other families with this disease were sought. In collaboration with Jane Kivlin, MD, of the Medical College of Wisconsin (Milwaukee), we used the same probe to study a multigeneration family from Utah. A different RFLP of 7.5 kb was identified after digestion with *Pvu* II restriction endonuclease; this RFLP mapped to the X chromosome and was inherited in an X-linked manner. A recombinational event between the OAT locus represented by this RFLP and the disease locus was observed (Figures 6 and 7). Linkage analysis of these two loci in this family revealed a maximum lod score of 1.88 at a recombination fraction of 0.10 (Table 8). Although both families have members affected with the same disease, the lod scores were reported separately because the 4.2- and 7.5-kb RFLPs may represent two different loci for the X-linked OAT sequences.[67]

The recombinational event found with the 7.5-kb RFLP indicates that the molecular defect of Norrie's disease is not within the sequence detected by this polymorphism. At present, however, we cannot exclude the possibility of a relationship between some of the OAT-related sequences represented by the 4.2-kb RFLP[66] and the disorder, as no recombinations have been identified. In view of the recombinations between the DXS7 locus represented by the L1.28 probe, the OAT locus represented by the 7.5-kb RFLP, and the Norrie's disease locus, the use of either or both the 4.2- and 7.5-kb RFLPs in addition to the L1.28 probe may increase the reliability and feasibility of identifying carriers and affected fetuses for prenatal diagnosis.

The identification of a common RFLP between the two families will allow the scores to be additive. A cumulative lod score of 3 or greater would establish the OAT as a new and useful DNA marker for Norrie's disease. These studies show the complexity that can be encountered when using candidate genes to identify cosegregation or linkage with a disease.

TABLE 7.—*Lod Scores for Norrie's Disease and the Human Ornithine Aminotransferase Complementary DNA**

	θ Values							
	0.000	0.010	0.050	0.100	0.200	0.300	0.400	0.500
Lod scores	0.602	0.589	0.536	0.470	0.338	0.211	0.096	0.000

*These are the recombination fractions for female members of the UCLA family studied. Because the genotypes identified by the 4.2-kb restriction-fragment-length polymorphism (RFLP) are known for each of the persons in this family, the estimate of the frequency of the RFLP was not required for the analysis. The frequency of Norrie's disease was assumed to be 0.0001 (from Ngo et al[66]).

TABLE 8.—*Lod Scores for Linkage Between Norrie's Disease and the Human Ornithine Aminotransferase (OAT) X-Linked Locus Detected by the 7.5-kb Restriction-Fragment-Length Polymorphism (RFLP)**

	θ Values						
	0.001	0.010	0.050	0.100	0.200	0.300	0.400
Lod scores	0.423	1.376	1.860	1.879	1.562	1.060	0.465

*The frequency of Norrie's disease in this Utah family was assumed to be 0.001. The frequency of the OAT allele represented by the 7.5-kb RFLP was calculated to be 0.345 based on female control subjects (from Ngo et al[67]).

We have also used the candidate gene approach to analyze large families with retinitis pigmentosa to identify cosegregation, linkage, or both. Biochemical studies described later by Dr Farber have suggested that the defect(s) in some of these disorders could be in the phototransduction pathway. Indeed, a mutation of rhodopsin has been shown in some patients with autosomal dominant retinitis pigmentosa.[1] We investigated a large kindred of three generations with more than 75 members affected with an autosomal dominant form of retinitis pigmentosa for RFLPs identified for the following candidate retinal specific genes: rhodopsin, transducin α_1 (rod specific), S antigen (48 kd), and interphotoreceptor retinol-binding protein. For each of the probes, an RFLP was identified in the family and mendelian inheritance shown. An RFLP of 1.2 kb was detected after digestion with *Rsa* I restriction endonuclease using the rhodopsin probe. Hybridization with the transducin α_1 probe after *Pvu* II restriction endonuclease digestion showed a pattern of four distinct bands of sizes 2.0, 1.8, 0.6, and 0.2 kb, with the 1.8-kb band being the RFLP. The interphotoreceptor retinol-binding protein probe detected 4.3- and 6.3-kb RFLPs with the *Bgl* II restriction endonuclease.[68] The S-antigen probe identified seven fragments with 3.9-kb and 4.3-kb polymorphisms.

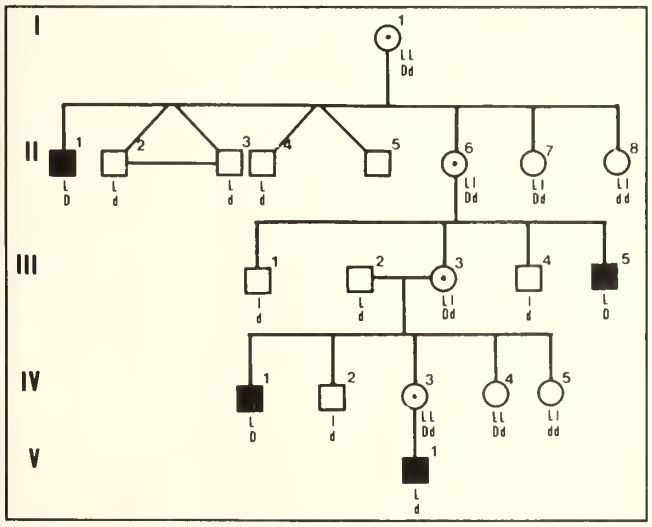

Figure 6.—The pedigree is from a 5-generation family affected with Norrie's disease. Members from whom DNA was obtained are identified with a number. Alleles identified with the L1.28 probe are designated as "L" or "I", allele "L" representing the 12.3-kb restriction-fragment-length polymorphism (RFLP) and allele "I" the 9.5-kb RFLP. Typing of this pedigree with the L1.28 has been reported by Kivlin et al.[53] Alleles identified with the human ornithine aminotransferase complementary DNA probe are designated as "D" for the presence of the 7.5-kb RFLP and "d" for the absence of the same fragment. Allele D cosegregates with the presence of Norrie's disease except for person V1, who is a recombinant affected offspring expressing the "d" allele; a recombinational event has occurred in person IV3 (from Ngo et al[67]; reproduced with permission from *Genomics*).

Lod scores were calculated, and cosegregation with the disease could be excluded for each of the candidate genes as the cause of the retinitis pigmentosa in this family. Linkage between the candidate gene and the disease was excluded for S antigen, transducin α_1, and interphotoreceptor retinol-binding protein. Although the lod score was low, linkage between the rhodopsin and the disease loci was suggestive. Because of the single crossover between rhodopsin and the disease loci, a mutation of the rhodopsin gene is unlikely in this family.

Although inconclusive, these studies show the practical value of the candidate gene approach for human studies and support the genetic heterogeneity of retinal degenerations. The retina is a specialized structure, and the spectrum of the response to insults is limited. The biochemical pathway for phototransduction is complicated, and defects in any of the proteins or enzymes involved in this pathway could lead to retinal degeneration. The future is promising for the identification and treatment of retinal diseases and other disorders of genetic origin.

Inherited Retinal Degeneration of the *rd* Mouse

Morphologic and Biochemical Findings

Dr Farber: The disease affecting the *rd* mouse retina begins early and progresses rapidly. At the light-microscopy level, no morphologic differences are found at 10 postnatal days between normal and *rd* mouse retinas, but at 13 days of age, the *rd* photoreceptors are degenerating rapidly, and by 20 postnatal days, most *rd* visual cells have died.[69] All other retinal cells, including the pigment epithelium, survive the disease.

Many years ago, we discovered a biochemical abnormality in the *rd* retina that is present before any morphologic abnormality is observed. As early as postnatal day 6, the

level of cGMP begins to rise above normal[70] due to a deficiency in the activity of cGMP-phosphodiesterase.[71] This reduced activity of the degradative enzyme of cGMP is restricted to the photoreceptor cells of the *rd* retina.[72] Other tissues of the *rd* mouse, such as blood—plasma, serum, lymphocytes, and erythrocytes—brain, muscle, and skin, have cGMP-phosphodiesterase activities comparable to those of control mouse tissues.

Cyclic GMP-phosphodiesterase is composed of four subunits, two with catalytic activity, α and β, and two identical γ subunits with inhibitory activity.[73,74] This enzyme is fundamentally important for phototransduction in rod photoreceptors. Its activation by light is mediated by components of the visual cell, including rhodopsin, transducin, and guanosine triphosphate.[75] Cyclic GMP-phosphodiesterase deactivation is also a complex process that requires the participation of other components of the photoreceptors, such as rhodopsin kinase, adenosine triphosphate (ATP), and a 4.8-kd protein also known as S antigen.[76]

We showed that cGMP-phosphodiesterase is synthesized normally by the *rd* photoreceptor cells and that there is no difference in the time of the onset of expression nor in the amount produced when compared with synthesis by normal mouse photoreceptors.[77] From the first time that cGMP-phosphodiesterase molecules are detected in the *rd* retina, however, and throughout the developmental period before visual cell degeneration, the cGMP-phosphodiesterase level is lower than in control retina. This suggests that the enzyme is more labile and becomes degraded soon after it is made. This could be due to one (or more) mutation occurring at the level of the DNA encoding the enzyme, which results in changes in the protein itself, or to the presence of a more active proteolytic system in the *rd* retina than in control retina.[77] Preliminary studies seem to indicate that the latter is not the case. Furthermore, cGMP-phosphodiesterase from *rd* retina is minimally activated by light,[78] which strengthens the possibility of a lesion in the enzyme itself or in any of the components of the photoreceptor cell involved in its activation or deactivation.

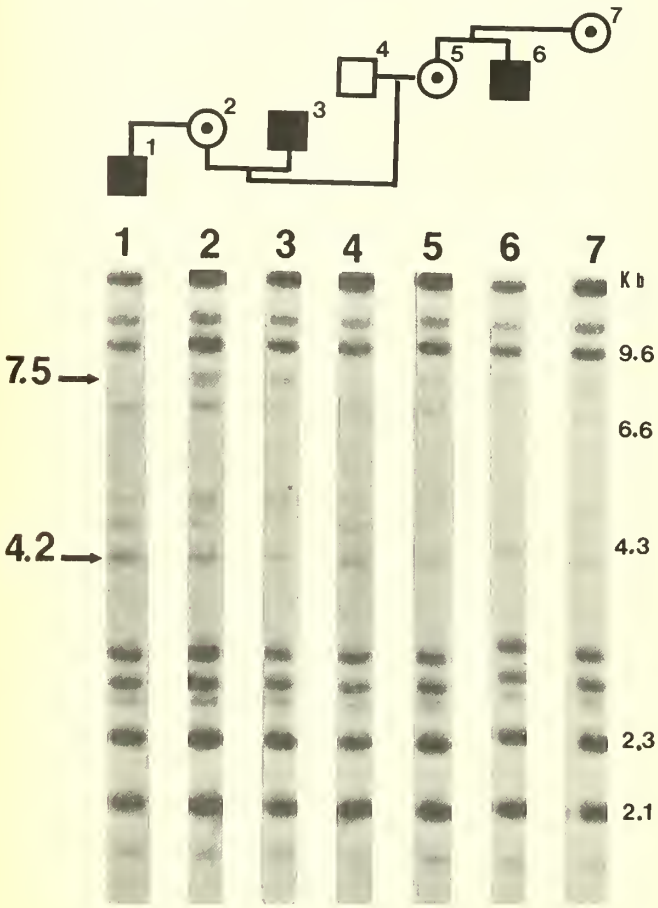

Figure 7.—A Southern blot hybridization pattern shows the distribution of the 7.5-kb restriction-fragment-length polymorphism (RFLP)-selected members of the 5 generations affected with Norrie's disease. Genomic DNA was digested with *Pvu* II endonuclease and hybridized to the human ornithine aminotransferase (OAT) complementary DNA probe. The 7.5-kb RFLP is identified by an arrow. Alleles identified with the human OAT cDNA probe are designated as "D" for the presence of the 7.5-kb RFLP and "d" for the absence of the same fragment. Allele "D" cosegregates with the presence of Norrie's disease except for person 1 (V1 of Figure 6) who is a recombinant affected offspring expressing the "d" allele; a recombinational event has occurred in person 2 (IV3 of Figure 6) (from Ngo et al[67]; reproduced with permission from *Genomics*).

Studies on the mRNAs encoding rhodopsin, the α, β, and γ subunits of transducin, the γ subunit of cGMP-phosphodiesterase and 48-kd protein, showed that these mRNAs are qualitatively normal in the *rd* retina and that they appear at the same time and are found in the same concentration as in control retina.[79-81] In addition, each of the proteins translated from these mRNAs has the same time of appearance in developing normal and *rd* retinas.[80] We concluded, therefore, that a delay in the expression of any of these six proteins involved in the activation or deactivation of cGMP-phosphodiesterase does not seem to be associated with the cause of the *rd* disease. Another abnormality of the *rd* retina was found, however, during the investigation of the functionality of rhodopsin: the visual pigment cannot be phosphorylated in vitro at any age, although it is present in concentrations comparable with normal until the photoreceptors start to degenerate.[82] Thus, we studied in normal and *rd* mouse retinas the activities of rhodopsin kinase, the enzyme that catalyzes the transfer of phosphate from ATP to rhodopsin, and of protein phosphatase 2A, the enzyme that dephosphorylates rhodopsin, because an excess of this activity could prevent the detection of phosphorylated rhodopsin. Our results confirmed the latter possibility.[83]

In previous investigations, we had examined the effect of several cations and nucleotides on the phosphorylation of rhodopsin in the outer segments of rod photoreceptors from normal retinas and showed that high levels of cGMP inhibited rhodopsin phosphorylation.[84] Our recent findings with the *rd* retina are consistent with the notion that the high cGMP concentrations present from early development in the *rd* photoreceptors may activate protein phosphatase 2A, a hypothesis that we are currently testing. This abnormality in the *rd* retina would then be secondary to the deficiency in cGMP-phosphodiesterase activity, which generates the elevated levels of cGMP.

Location on Mouse Chromosomes of Candidate Genes for the rd *Mutation*

The *rd* gene has been localized on mouse chromosome 5.[85] To confirm that none of the proteins involved in the activation or deactivation of cGMP-phosphodiesterase are the site of the *rd* locus, we determined the chromosomal location of the corresponding cDNAs and of all other retinal cDNAs that became available to us. These studies were carried out using hamster-mouse somatic cell hybrids and

TABLE 9.—*Assignment of Some Photoreceptor Genes to Mouse Chromosomes*

Gene	Mouse Chromosome
Rhodopsin	6
Transducin α_1*	9
Transducin β†	4
S antigen‡	1
cGMP-PDEα§	18
cGMP-PDEγ‖	11

cGMP-PDE = cyclic guanosine monophosphate-phosphodiesterase

*From Danciger et al.[86]
†From Danciger et al.[87]
‡From Danciger et al.[88]
§From Danciger et al.[89]
‖From Danciger et al.[90]

mouse interspecific backcrosses. Table 9 summarizes our results.[86-90] Indeed, we did not assign any of the other genes investigated to mouse chromosome 5. This indicates that none of the proteins encoded by these genes is the primary lesion of the *rd* disease.

Identification and Cloning of a Candidate cDNA for the rd *Gene*

At the same time that these studies were carried out, we began to search for the *rd* gene with a totally different approach. Our strategy was based on the assumption that the mRNA encoded by the *rd* gene would be either absent or expressed in greater or lesser amounts in normal than in affected *rd* photoreceptors.

We took advantage of the fact that the retina of the adult *rd* mouse has no photoreceptor cells and is constituted solely by the inner retinal layers, to subtract the cDNAs of these inner retinal layers from the cDNAs of a normal retina. This allowed us to obtain a pool of 588 photoreceptor-specific cDNAs. These clones were screened for the *rd* gene by differential hybridization, using single-stranded retinal cDNAs from 9- to 11-day-old, morphologically normal, $rd/^+$ mice and single-stranded retinal cDNAs from their affected *rd/rd* littermates. The greatest amount of age-matched retinal tissue can be obtained at this age, before full degeneration of the *rd/rd* visual cells. We found three clones that hybridized differently with the two probes. When the DNA of these three clones was used, however, to probe Northern blots containing normal and *rd/rd* mouse retinal RNAs, only one clone, zr.408, hybridized more faintly to the *rd/rd* RNA than to the age-matched normal RNA.[3]

We characterized the zr.408 cDNA, and from its properties we inferred that it was a strong candidate for the *rd* gene. The zr.408 clone hybridized a 3.3-kb mRNA from normal retina and only weakly a larger 3.6 kb from *rd/rd* retina. This size difference could result from alternative splicing, polyadenylation site differences, or the presence of a structural alteration in the corresponding gene of the *rd/rd* mouse. In addition, zr.408 hybridized to the DNAs from somatic cell hybrids, permitting us to map the corresponding gene to mouse chromosome 5. The zr.408 clone hybridized different-sized restriction fragments from genomic normal ($^+/^+$) and *rd/rd* DNAs, suggesting a structural difference between the $^+/^+$ and *rd/rd* gene sequences at sites homologous to zr.408. This was further confirmed by the fact that $^+/^+$ and *rd/rd* polymorphisms were present in the $rd/^+$ DNA at about half the intensity found for each in the DNAs from the homozygous mice. Finally, the mRNA hybridized by zr.408 was detectable on postnatal day 1 in normal and *rd/rd* retinas; its concentration increased steadily during development but was always lower in the *rd/rd* retina. Following the degeneration pattern of the *rd* retina, the levels of zr.408 mRNA decreased sharply by 14 postnatal days and were no longer detectable at 31 days of age. Thus, the expression of the candidate *rd* cDNA is abnormal in the *rd/rd* retina several days before cGMP levels become elevated in the visual cells. This is the earliest molecular lesion that has been shown in the *rd* mouse disease.[3]

To further confirm that zr.408 does in fact correspond to the *rd* gene, we undertook two molecular genetic studies. The aim of the first was to verify that the gene corresponding to zr.408 and the *rd* gene map to the same location on mouse chromosome 5. The second project was designed to show cosegregation of the candidate *rd* gene with the expression of the *rd* disease, photoreceptor cell degeneration. We carried out these studies using interspecies backcrosses, which have been shown to give RFLPs more frequently than mouse inbred crosses.

In an interspecies backcross, a wild mouse and an inbred mouse are mated. All the resulting F1 offspring are heterozygous for every gene. The F1 animals are then backcrossed either with wild or inbred mice, and the progeny consist of animals homozygous or heterozygous for specific genes. If two genes being investigated are close together on a chromosome, few recombinants will be produced. From the rate of recombination, it is possible to estimate the distance in centimorgans at which the two genes are located.

The DNAs from the NFS/N and *Mus mus musculus* mice were analyzed for RFLPs that hybridized to the zr.408 probe. These RFLPs were then identified in DNAs from 62 backcrossed progeny of the cross (NFS/N × *M m musculus*)F1 × *M m musculus*. The inheritance pattern of the gene corresponding to zr.408 was compared with the inheritance patterns of two other genes that lie on opposite sides of the *rd* gene on mouse chromosome 5, *Afp* and *Gus*. By determining the number of backcrossed progeny heterozygous for zr.408 and homozygous for *Afp* or *Gus*, or vice versa, we could establish the number of recombinants present.[91] This permitted us to position zr.408 between *Afp* and *Gus* at distances similar to those established for the *rd* gene with respect to *Afp* and *Gus* on standard chromosome maps (V. M. Chapman, W. K. Noell, D. Adler, *Mouse Newsletter*, 1975, volume 53, p 61).

For our cosegregation study, DNAs from C57BL/6J *rd/rd* and *Mus spretus* mice were analyzed for RFLPs that hybridized to the zr.408 probe. These RFLPs were then examined in DNAs from 72 backcrossed progeny of the cross (C57BL/6J *rd/rd* × *M spretus*)F1 × C57BL/6J *rd/rd*. The animals homozygous and heterozygous for zr.408 were identified. These results were then compared with the histologic results showing the presence or absence of retinal degeneration obtained by examining the retinas of the 72 backcrossed mice. We found that zr.408, the candidate *rd* gene, cosegregated with the *rd* disease with no recombinants obtained, that is, each of the assignments to *rd/rd* or $rd/^+$ determined by blot hybridization with zr.408 corresponded exactly to the histologic identification.[91]

The results described offer strong evidence for zr.408 corresponding to the *rd* gene. We have recently determined the nature of its expressed product. This gene encodes the β

subunit of cGMP-phosphodiesterase,[92] which explains our previous findings.

Histopathologic and Biochemical Findings on Human Eyes Affected With Autosomal Dominant Retinitis Pigmentosa

We studied the eyes of a 17-year-old boy affected with autosomal dominant retinitis pigmentosa who died in a motorcycle accident. He had been examined by an ophthalmologist when he was 15, at which time he had a loss of night vision. Although his visual acuity was normal, his fundi had the typical appearance of retinitis pigmentosa. His electroretinogram showed that the scotopic and photopic responses were barely recordable.

The eyes of this donor were enucleated within an hour after death. The right eye was fixed for morphologic[93] and immunocytochemical studies, and the left eye was frozen at −80°C and used for biochemical studies.[94]

Light-microscopic analysis of the retina showed photoreceptor cell degeneration increasing from the fovea to the equatorial area and then decreasing toward the periphery. We counted the number of rods and cones throughout the retina and compared the results with those obtained from a normal human retina of similar age used as reference. The superior temporal quadrant was the least affected, its periphery retaining about 40% of the rods present in the same quadrant of the normal retina. The periphery of the other three quadrants had pronounced reductions in the number of rod cells, the superior nasal quadrant retaining 19% rods, the inferior nasal 11%, and the inferior temporal practically none. In addition, no rods were present in the equatorial region of the retina. Although the cone population suffered less drastic reductions, with a loss of about 25% of the foveal cones, there were no cones left in the equatorial region of the retina. The retinal pigment epithelium showed no unusual accumulation of lipofuscin or debris, and the cells of the inner retina remained unchanged.

For the biochemical studies, the frozen eye was cut into four quadrants, which were dissected in an ultramicrotome maintained at −30°C. After removing the vitreous, we took sequential 3-mm retinal punches from each quadrant, ensuring the analysis of every piece of retina. The features that we measured in each punch of the retina were all those investigated previously in the *rd* mouse. We found that cGMP-phosphodiesterase activity was lower than normal throughout the retina and that there was minimal or no detectable activity in the most central and equatorial regions. Except for a portion of the periphery of the superior temporal quadrant where the level of cGMP-phosphodiesterase was reduced by 10%, all the rest of the peripheral retina had 25% to 45% of the activity present in comparable regions of the age-matched normal retina.

We studied the phosphorylation of rhodopsin in punches of retinitis pigmentosa retina that contained rod photoreceptors and rhodopsin. As with the *rd* mouse, we could not detect the incorporation of phosphorus 32 (from ^{32}P-ATP) into rhodopsin.

The greatest difference between the retina with retinitis pigmentosa and the normal one was found in the pattern of distribution of cGMP, which concentration was much reduced in all areas. Cyclic GMP is localized mostly in rods,[95] and the cells of the inner retina do not contribute substantially to cGMP levels.[96] Taking advantage of this specific localization and of our measurements of the number of rods in every square millimeter of the normal and affected retinas, we estimated the cGMP concentration per photoreceptor cell in all areas of each quadrant. Normal visual cells contained similar amounts of cGMP throughout the retina, which ranged between 2 and 4×10^{-18} mol per rod. An exception to this was the fovea, which had minimal or no cGMP. In contrast, the photoreceptors of the affected retina contained high levels of cGMP in specific areas: about 40-fold to 100-fold higher than normal levels in the few outer segment-devoid rods of the postequatorial region and in the periphery of the inferior temporal quadrant and 15-fold to 20-fold higher than normal levels in the rods from the area close to the periphery of the superior temporal quadrant. The rest of the peripheral retina had twofold to threefold higher than normal levels of cGMP per visual cell. No other retinal punches contained measurable cGMP, correlating with the loss of rod photoreceptors.

Therefore, the same biochemical abnormalities found in the *rd* mouse retina were present in this autosomal dominant case of retinitis pigmentosa. These findings leave open the possibility that a similar mechanism may be responsible for the degeneration of the visual cells in the diseases affecting the *rd* mouse and the dominant type of human retinitis pigmentosa. We are currently carrying out molecular biologic studies that will confirm or rule out such a hypothesis.

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Vibrio vulnificus

Hazard on the Half Shell

KRISTI L. KOENIG, MD, *Orange;* JUERGEN MUELLER, MD; *and* THEODORE ROSE, MD, *Oakland, California*

Vibrio vulnificus is an extremely invasive gram-negative bacillus that causes bacteremia and shock. It should be suspected in any patient who is immunocompromised or has liver disease or hemochromatosis. Reduced gastric acidity may also increase the risk of infection if a patient presents with a history of ingesting raw shellfish (especially oysters) or trauma in brackish waters and skin lesions. Patients most commonly present with one of three clinical syndromes: primary septicemia, wound infection, or gastroenteritis. Treatment includes aggressive wound debridement, antibiotic therapy, and supportive care. Rapidly diagnosing and promptly initiating therapy are critical because *V vulnificus* infection is rapidly progressive and mortality approaches 100% if septic shock occurs.

(Koenig KL, Mueller J, Rose T: *Vibrio vulnificus*—Hazard on the half shell. West J Med 1991 Oct; 155:400-403)

Vibrio vulnificus is an increasingly recognized cause of sepsis that occurs in patients with preexisting liver disease or immunocompromised states who have recently ingested raw seafood. Because of dietary trends, this at-risk patient population may be eating increasing amounts of shellfish without awareness of the associated risks. *V vulnificus* infection is rapidly progressive and deadly if not recognized promptly and treated aggressively.

This review was prompted by the case of a patient who presented with *V vulnificus* sepsis after ingesting raw oysters shipped from Louisiana to her home in northern California.

History

Vulnificus comes from the Latin word for "wounding"—an appropriate name, as this species of *Vibrio* may cause extensive soft tissue damage. Hippocrates described what may be the first case in the medical literature. A patient named Criton from the island of Thasos presented with "violent pain in foot," fever, delirium, and black blisters of his skin.[1] Despite state-of-the-art therapy, he died on the second day after the onset of symptoms. As Criton was a fisherman, it is likely that he was exposed to the organism in seawater.

The first recent report of clinical infection was in 1970, with the case of a previously healthy man in whom leg gangrene, a generalized hemorrhagic rash, thrombocytopenia, hypotension, and vomiting and diarrhea developed two days after he bathed and clammed in the seawater of Narragansett Bay.[2] Although *Vibrio vulnificus* was first isolated by the Centers for Disease Control in 1964,[3] the patient's symptom complex was initially mistakenly attributed to *Vibrio parahaemolyticus*. *Vibrio vulnificus* was first given its name in 1979.[4,5]

Epidemiology

The peak incidence of cases is in the summer months, with a range from March to November.[6-8] The male-to-female ratio is 4 to 1; more than 90% of patients are older than 40 years; and more than 90% of patients have eaten raw or undercooked oysters within 24 to 48 hours of clinical infection (range 7 hours to 4 days).[9,10] The amount of oysters consumed ranges from 3 to 48.

The organism is halophilic (salt-loving); it will not grow in a saltfree environment. *V vulnificus* is most frequently isolated from seawater with a temperature greater than 20°C (68°F) and a salinity of 0.7% to 1.6%, and it is rarely found in seawater cooler than 17°C (62.6°F).

Surveys have shown that more than 50% of oysters and 10% of crabs are culture-positive for this organism.[11,12] Culture-positivity is highly seasonal, with oysters most likely to be positive during warm summer months.[13] The incidence of *V vulnificus* infection is not increased with fecal contamination of seawater, and, in fact, the organism may grow better in the absence of enteric bacteria. It will proliferate in seafood kept at room temperature but will be killed by boiling or freezing.[9]

Vibrio vulnificus has been found in virtually every geographic location in the United States, including seawater in the Gulf of Mexico, off both coasts, as far north as Cape Cod, and off the islands of Hawaii.[14] It has been found in lakes in New Mexico and Oklahoma and from the Great Salt Lake in Utah. In general, Pacific shellfish have not been implicated as causes of disease in humans. Cases have been reported from Japan, Belgium, and Australia, but most reported cases are from the United States.

Pathophysiology

Vibrios are motile, curved, rod-shaped, gram-negative bacteria. *Vibrio vulnificus* is an extremely invasive organism that commonly causes bacteremia and shock. It may invade vascular endothelium and create a necrotizing vasculitis[15-17] leading to endothelial hypoplasia and septic thrombosis.

Bullae are common and result from dermal necrosis, which is thought to be due to the extracellular toxins produced by this bacterium.[18] Subcutaneous tissue, muscle, and nerves may be completely destroyed in the course of this infection.

From the Division of Emergency Medicine, University of California, Irvine, Medical Center, Orange (Dr Koenig), and the Department of Medicine, Highland General Hospital, Oakland, California (Drs Mueller and Rose).

Reprint requests to Kristi L. Koenig, MD, Assistant Adjunct Professor of Medicine, Division of Emergency Medicine, University of California, Irvine, 101 City Dr, Route 128, Orange, CA 92668.

Iron appears to be needed for the growth of *V vulnificus*.[6,19,20] Studies using animals show the median lethal dose for organisms producing sepsis will be lowered if iron is given as a premedication. *Vibrio* species are able to extract iron from hemoglobin and use it as a nutrient. The elevated serum and tissue iron levels, with the saturation of transferrin, found in patients with liver disease may provide a nutrient substrate for the proliferation of *Vibrio* organisms.

Several other theories exist as to why morbidity is increased in the presence of liver disease. The shunting of portal blood containing *V vulnificus* infection around a diseased liver may lead to septicemia.[13] Poor opsonization and a reduced activity of polymorphonuclear leukocytes and Kupffer's cells in the diseased liver may lead to a decreased clearance of bacteria from the portal circulation.

The common occurrence of hypotension is thought to be due to several toxins produced by the pathogenic *V vulnificus*. A cytolysin has been shown to be hemolytic in animals and causes a disruption of collagen and damage to capillary endothelium.[21] The organism is also known to produce elastase,[22] collagenase,[23] and phospholipase.[24] A capsule is present that resists phagocytosis and bactericidal activity of human serum. This is genetically determined, and its presence correlates directly with the virulence of the organism. Strains can undergo phase variation, shifting between encapsulated and unencapsulated forms.

The organism may occasionally be identified in wound or bullae fluid and stool, as well as blood specimens, in patients with sepsis.[25] The use of a selective medium such as thiosulfate citrate bile salts is usually necessary. The laboratory should be notified that *V vulnificus* is suspected because identification of the organism can be difficult (especially from stool specimens).[26,27]

Risk Factors

Certain groups of patients have been shown to be at greater risk for complications after exposure to *V vulnificus*. It is rare for a person without a risk factor to be affected.

High-risk patients include those with:

- Liver disease and other diseases with possible hepatic involvement or elevated serum iron levels (including cirrhosis, alcoholism, malignancy, hemochromatosis, or thalassemia major)[3,28-30];
- Therapeutically induced or naturally low gastric acid (achlorhydria or antacid or H_2 blocker use)[26,31];
- Compromised immune systems (patients with the acquired immunodeficiency syndrome [AIDS] or AIDS-related complex; patients with cancer, especially during treatment; patients with diabetes mellitus; and patients with renal disease, chronic intestinal disease, or steroid dependency).[29,30]

In one study, only 17% of patients in high-risk groups were aware of the danger associated with ingesting raw seafood.[32] This emphasizes the important role of physicians in educating certain patient populations.

Clinical Presentation

Three clinical syndromes have been reported: primary septicemia, wound infection, and gastroenteritis.[7,14,19,33] In the largest review to date,[7] a report of 62 cases in Florida between 1981 and 1987, the group of patients with septicemia was the largest (62% of the total). The patients' mean age was 62, and 87% were male. This syndrome was characterized by the abrupt onset of fever and chills with secondary skin lesions arising within 24 hours in more than half of the patients. Intense lower extremity pain, vomiting, diarrhea, and abdominal pain were all common complaints. Cultures of blood were positive for *V vulnificus* in 97% of these patients. Various other cultures were also positive, including cultures of cerebrospinal fluid. The overall mortality for these patients was 55%, although the mortality in patients with hypotension during the first 48 hours of illness was 92%. Of these patients, 66% had underlying liver disease and 5% had hemochromatosis. Liver disease or other chronic illness was diagnosed in 95%.

The other two syndromes made up a relatively minor percentage of cases. Wound infections were evident in 27%

TABLE 1.—*Signs and Symptoms of* Vibrio vulnificus *Infections**

	Patients, %		
Signs and Symptoms	*Primary Septicemia, 62%*	*Wound Infection, 27%*	*Gastroenteritis, 11%*
Systemic	100†	70†	70†
Fever	94	75	57
Chills	91	39	43
Mental status changes	50	18	0
Hypotension (systolic blood pressure <90 mm of mercury)	35	14	0
Gastrointestinal	71†	12†	100†
Nausea	58	NA	NA
Vomiting	35	12	29
Abdominal pain	34	0	100
Diarrhea	30	3	100
Cutaneous Lesions	75†	100†	0†
Cellulitis	50	90	0
Bullae	40	38	0
Ecchymosis	32	20	0
Bacteremia	100	30	NA
Mortality	55‡	25	0

NA = data not available

*Modified from Klontz et al.7
†Percent of patients with at least one of the listed signs or symptoms.
‡More than 90% of patients are in shock.

TABLE 2.—*Bullous Skin Lesions With Sepsis: Differential Diagnosis*
Group A streptococcal erysipelas with necrotizing fasciitis (gangrenous erysipelas)
Ecthyma gangrenosum (due to *Pseudomonas aeruginosa* or *Aeromonas*)
Vibrio infections, including *Vibrio vulnificus*
Staphylococcal cellulitis
Streptococcal cellulitis
Toxic epidermal necrolysis (staphylococcal scalded skin syndrome, infections, medications)

TABLE 3.—*Management of* Vibrio vulnificus *Infections*
History: Raw shellfish ingestion? Contact with seawater? Risk factors?
Cultures: Take specimens of blood, wounds, and stool for culture; notify laboratory of suspected *V vulnificus* infection
Antibiotics: Tetracycline (with or without gentamicin or chloramphenicol) therapy promptly
Supportive care: Monitoring in intensive care unit, fluids, watch for complications (disseminated intravascular coagulation, bleeding, shock)
Surgical treatment: Aggressive debridement of wounds, consider amputation
Reporting: Legally notifiable condition to public health department

TABLE 4.—*Educational Instructions for the Prevention of* Vibrio vulnificus *Infection*
Immunocompromised patients: Avoid raw or improperly cooked shellfish
Patients with cutaneous lesions: Avoid contact with seawater
Public: Warning labels on shellfish containers and menus, public health brochures

of the patients. More than 80% of these had direct contact with seawater on open wounds. Blood cultures were positive in only 30% of these patients, with a correspondingly lower mortality of 24%.

Only 11% of patients presented with the third clinical syndrome: gastroenteritis characterized by vomiting, diarrhea, and abdominal pain with a stool culture positive for *V vulnificus*. None of the patients in this group died.

Two other large reviews of 39[13] and 23 patients[19] yielded similar results to those of the series described above. There are about 20 other case reports in the literature that emphasize the wide spectrum of disease processes caused by *V vulnificus*. These include pneumonia and septicemia following the aspiration of seawater,[34] meningitis,[7] spontaneous bacterial peritonitis,[35,36] endometritis after intercourse in seawater,[37] necrotizing fasciitis[15,16] presenting with compartment syndrome,[17] corneal ulcers,[38] epiglottitis,[39] and infections of the testes, spleen, and heart valves.[6,14]

Overall, 94% of patients present with fever, 91% with chills, 75% with skin lesions, and 58% with nausea (Table 1).[1] A third of patients are in shock when they are first seen, or hypotension develops within 12 hours of admission,[4] and more than 90% of these will die.[11] Patients may present with severe, localized pain that precedes the onset of skin lesions by hours to days.[1,13]

Distinct bullous skin lesions, which develop secondary to sepsis, are present in about 40% of patients.[4,11,40] The differential diagnosis of these lesions includes group A streptococcal erysipelas with necrotizing fasciitis (gangrenous erysipelas), ecthyma gangrenosum secondary to *Pseudomonas aeruginosa* or *Aeromonas* species, other *Vibrio* species infections, brown recluse spider bites, and staphylococcal or streptococcal cellulitis (Table 2).[6,41]

Thrombocytopenia is common, and there is often evidence of disseminated intravascular coagulation.[4,12,35] Leukopenia is more common than leukocytosis. Other complications include the respiratory distress syndrome and heart block.

Management

Once *Vibrio vulnificus* is suspected, appropriate cultures (of blood, wound or bullae, and stool specimens) should be done and aggressive management begun immediately. Supportive care with intravenous fluids (and pressors if needed) and monitoring in an intensive care unit are essential. Careful observation for possible complications such as disseminated intravascular coagulation is crucial.

Treatment with antibiotics must be initiated promptly. The organism is susceptible to a wide variety of antibiotics in vitro (tetracycline, erythromycin, ampicillin, cephalosporin, chloramphenicol, norfloxacin, and gentamicin). In studies of mice, however, ampicillin, cephalosporin, erythromycin, and gentamicin are not as effective as tetracycline.[42] Tetracycline is currently recommended as the drug of choice.[10,20] The addition of an aminoglycoside[7] or chloramphenicol[19] is often advised.

It has been shown that case-fatality rates for patients with septicemia increase with greater delays between the onset of illness and the initiation of antibiotic treatment or if tetracycline is not used in the regimen.[7]

Along with supportive care and the prompt administration of antibiotics, the third component of treatment is aggressive wound care. Debridement of wounds is essential,[12] and amputation of the affected limb may be life-saving in some cases (Table 3).[43]

As of May 1, 1988, infection due to *Vibrio* species is a legally notifiable condition in California.[9]

Clinical Implications

Although early treatment with antibiotics has some efficacy, the mortality associated with septicemia remains high, emphasizing the need for education to prevent this disease

from occurring (Table 4). Clinicians should warn immunocompromised patients (including those infected with the human immunodeficiency virus) to avoid eating raw seafood.

If the prevention of *Vibrio* infection is not possible, physicians must maintain a high index of suspicion to identify patients at risk. The diagnosis should be entertained when a high-risk patient presents with upper or lower extremity skin lesions, especially if a history of eating shellfish is elicited. The disease is rapidly progressive and must be treated aggressively. Appropriate specimens for culture should be obtained, antibiotic therapy begun, and blood pressure support initiated.

Summary

There are two major syndromes of *Vibrio vulnificus* infection. One of these is primary septicemia, which is usually seen in patients with underlying liver disease who have eaten raw oysters 24 to 48 hours earlier. The syndrome is characterized by fever, chills, nausea, and characteristic lower extremity lesions. Hypotension is present on admission in more than a third of bacteremic patients. Skin lesions are present in 75%, usually consisting of bullae, although pustules, petechiae, and purpura may also be seen. The syndrome of septicemia carries a mortality rate in excess of 50%,[26,27] which approaches 100% if hypotension occurs within 12 hours of admission.[35]

The second major syndrome is that of a wound infection, usually seen in a healthy person in whom a wound develops while cleaning shellfish or who has an existing wound that is exposed to seawater. Only a third of these patients have positive blood cultures,[1] and the mortality is about 25%. Patients who have underlying health problems such as liver disease or malignancy are more likely than healthy persons to have disseminated infection develop.

The early recognition of these syndromes and appropriate antibiotic therapy followed by local supportive measures are the key to reducing the impressive mortality associated with *V vulnificus* infection.

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Epitomes

Important Advances in Clinical Medicine

General Surgery

The Scientific Board of the California Medical Association presents the following inventory of items of progress in general surgery. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome, and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, researchers, or scholars to stay abreast of these items of progress in general surgery that have recently achieved a substantial degree of authoritative acceptance, whether in their own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on General Surgery of the California Medical Association, and the summaries were prepared under its direction.

Reprint requests to Division of Scientific and Educational Activities,
California Medical Association, PO Box 7690, San Francisco, CA 94120-7690

Advances in the Management of Hemorrhagic Shock

Hemorrhagic shock occurs when extensive blood loss leads to reduced oxygen delivery and, hence, cellular oxygenation inadequate to meet metabolic demands. This oxygen deficiency results in the disruption of cellular function and, subsequently, cellular structure. Resuscitation is complete only when oxygen delivery is sufficent to satisfy metabolic requirements. Therapeutic end points have classically consisted of the restoration of normal vital signs and organ function. Recent investigation, however, suggests that the active use of other monitoring criteria more related to oxygen delivery and consumption leads to a better outcome.

The major initial physiologic problem in hemorrhagic shock is a depletion of the intravascular volume. This limits cardiac filling and leads to diminished stroke volume, cardiac index, and oxygen delivery, resulting in tissue ischemia. Secondary perpetuators of tissue ischemia are important and include vasoconstriction, intravascular aggregation, and microthrombosis. All of these microcirculatory alterations limit oxygen delivery. A tertiary perpetuator of the pathophysiology is reperfusion injury. This occurs on the restoration of circulation to ischemic tissues, which leads to the formation of extremely toxic superoxide radicals. The end result of these processes is ischemic tissue damage, an inflammatory tissue response, and a hyperdynamic and hypermetabolic state. In addition, B and T lymphocytes, macrophages, and polymorphonuclear leukocytes all function abnormally in the shock state. This results in a susceptibility to septic complications that greatly exacerbates the altered physiology.

To treat hemorrhagic shock, it is important to understand the physiologic alterations determining tissue oxygen delivery. There are three primary determinants of tissue oxygenation: cardiac output, arterial oxygen content, and mixed venous oxygen content. Oxygen extraction (oxygen consumption/oxygen delivery), an indirect measure of use, is 25% in the resting state and can triple in a healthy person under demanding circumstances. Shock-induced alterations in microcirculatory blood flow and cellular injury, however, impair this metabolic compensation. Elevated circulating catecholamines and primary neurogenic effects cause uneven microvascular vasoconstriction, interfering with oxygen distribution. In shock, there is a tendency for erythrocytes to form into rouleaux and for platelets and leukocytes to adhere to capillary endothelium. In addition, thrombi form more frequently within constricted capillaries. All of these dynamics decrease the amount of oxygen delivered. Mitochondrial dysfunction accompanying shock also obstructs oxidative phosphorylation, limiting cellular aerobic metabolism.

Treatment is best directed at the underlying pathophysiology rather than the classically monitored end points. Blood pressure and urine output are insensitive in reflecting the microcirculatory flow disturbances compared to variables of tissue oxygenation. Because a small amount of oxygen is dissolved in plasma, hemoglobin saturation is more important than oxygen tension in contributing to arterial oxygen content. Therefore, unless severe anemia or hypoxia exists, supplemental oxygen adds little to tissue delivery. Transfusion to supranormal hemoglobin concentrations is not advisable in resuscitation as this encourages microcirculatory sludging and impaired oxygen release to tissues due to a diminished 2,3-diphosphoglycerate content. Even transfusion to normal hemoglobin levels may be counterproductive because of increased resistance in the altered microcirculation. Indeed, reduced viscosity at lower hematocrits may enhance microcirculation and oxygen delivery. Many patients can tolerate hematocrits as low as 0.20 (20%) as long as they are given adequate volume replacement; elderly patients and those with coronary artery disease are usually stable at 0.30 (30%). As oxygen therapy and blood transfusion are often not indicated, the major approach available to enhance oxygen delivery is to increase the cardiac output.

The cardiac output is determined by preload, afterload, contractility, and heart rate. The treatment of preload is usually the most important initial therapy in the emergency setting, as most patients in shock have physiologic tachycardia. It is inappropriate to use inotropic agents until optimal preload is ensured; the use of α-adrenergic drugs aimed at raising the blood pressure is contraindicated. Thus, intravenous fluid therapy to optimal preload levels is the mainstay of initial management. Various modalities aimed more directly at the cellular pathophysiology are under investigation.

Promising approaches address vasoconstriction, tissue inflammation, cellular aggregation, and reperfusion injury.

The goal of therapy ought not to be simply restoring vital signs. Rather, the aim should be to restore effective oxygen delivery and use. Understanding the physiology of oxygen transport aids in choosing therapy and administering it to the best end points.

SCOTT R. MILLER, MD
KENNETH WAXMAN, MD
Irvine, California

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Use and Abuse of Parenteral Nutrition

SINCE THE INTRODUCTION of safe and nutritionally effective total parenteral nutrition (TPN) in the late 1960s, this therapy has been enthusiastically accepted as a major advance in the management of patients unable to eat. Despite nearly 25 years of study, however, many of the judgments derived intuitively or from retrospective reviews have not yet and may never pass the scrutiny of randomized, controlled prospective analysis, in part because of the ethical considerations arising from the need for an unfed control group. Thus, parenteral nutrition remains an apparently potent therapeutic modality used primarily on the basis of clinical judgment and experience and only secondarily on the basis of prospective statistical data.

Although TPN and enteral feedings are nutritionally comparable, enteral nutrition is usually considered preferable when feasible, primarily because it is less expensive. In addition, recent experimental data suggest that enteral feedings may prevent the bacterial translocation sometimes associated with the gut atrophy that occurs in patients receiving TPN. These advantages of enteral nutrition are blunted, however, by the surprisingly high incidence of pulmonary aspiration during tube feedings and the dramatic reduction in complications with TPN in recent years. For many patients, however, TPN is the only option because of conditions that preclude alimentary tract nutrition for more than seven to ten days. For normally nourished patients unable to eat for shorter periods, the protein-sparing effect of 100 to 150 grams of glucose provided in a 5% solution is sufficient.

In some patients, parenteral feedings appear to have benefits in addition to their nutritional effects. The reduced mechanical and secretory activity of the alimentary tract induced by TPN may be valuable in managing inflammatory diseases, such as pancreatitis and regional enteritis. Total parenteral nutrition, often with the concomitant administration of somatostatin, is essential in the management of acute enterocutaneous fistulas. Similarly, patients with the short bowel syndrome all receive TPN initially, and some patients require prolonged or indefinite therapy. In patients with severe malnutrition who require an elective operation, the preoperative administration of TPN for seven to ten days appears to reduce postoperative morbidity and mortality.

During pregnancy, intravenous nutrition provides important benefits to the fetus, including a reversal of subnormal fetal growth, when intractable hyperemesis gravidarum develops or the woman is otherwise nutritionally compromised. In addition, preliminary reports indicate that TPN provides some specific benefits to patients having liver or bone marrow transplantation. In contrast, specific benefits of TPN in acute renal failure have not been confirmed. While TPN is valuable for cancer patients when malnutrition precludes adequate antitumor therapy, its synergistic effect on the efficacy of chemotherapy or radiotherapy noted in some animal experiments unfortunately has not been shown in humans. Nutrient solutions enriched with the branched-chain amino acids, so attractive in theoretic models of hepatic encephalopathy and hypermetabolic critical illness, also have not proved clinically useful. Administering TPN that provides calories in excess of requirements for energy expenditure or nutritional repletion is contraindicated because of adverse effects on the liver and pulmonary function and no demonstrable nutritional benefit.

With the development of lipid-based infusions that can provide all required nutrients by a peripheral vein, hypocaloric "protein-sparing" regimens are no longer useful. When a nutritional repletion of chronically malnourished patients is undertaken, therapy must be gradual to avoid a series of "refeeding syndromes," including hypokalemia, hypophosphatemia, hypomagnesemia, acute thiamine deficiency, and congestive heart failure. Total parenteral nutrition is not indicated for hopelessly ill patients for whom no effective primary therapy is available, unless the nutritional support provides an improved sense of well-being or substantial psychological palliation.

HOWARD SILBERMAN, MD
Los Angeles, California

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Procuring Donor Organs for Transplantation

THE DEMAND FOR transplantable organs increasingly exceeds the supply as transplantation programs and organ recipient criteria expand. Potential donor organ availability has been estimated to be at least two to three times actual procurement rates. The 6%-a-year mortality for the 18,000 to 20,000 patients on the transplant waiting list could be reduced by identifying and correcting problems in the organ procurement process.

The four principal steps that must be completed before organs can be recovered include identifying and screening potential organ donors, formally declaring brain death, obtaining consent for organ donation from next of kin, and physiologically maintaining donor cardiopulmonary and renal function to retain optimal organ function.

Most organ donors can be identified early in their hospital course. In general, patients younger than 70 years with isolated, nonsurvivable central nervous system injury or disease should be considered possible organ donors. The premature limitation or withdrawal of support from this group by well-meaning but uninformed or disinterested physicians accounts for a large number of "lost" donor organs, particularly in

community hospitals. To avoid this type of procurement failure, most states have adopted various forms of required request laws. These laws are designed to ensure that family members are given the option of donating a relative's organs and tissues. They vary in their specifics from so-called weak request laws requiring only that hospitals have in place policies ensuring that some request was made, to "strong" laws that require formal documentation of requests and responses. Recognizing that these laws are difficult to enforce, changes in policies of the Joint Commission on the Accreditation of Healthcare Organizations and Health Care Financing Administration regulations have been enacted to encourage hospitals to provide support for organ procurement programs.

A failure to obtain consent has been responsible for 40% to 70% of losses of otherwise eligible donors. Three recent trauma center studies have found next-of-kin consent rates of 64%, 57%, and 54%. This is at variance with a recent Gallup poll reporting an 82% favorable response rate to the subject of next-of-kin organ donation. The reasons for this discrepancy are complex and involve cultural differences, professional attitude and interests, and timing. Many believe that requests for organ donation are best made by professionals who are trained to do so and who do not have direct patient care responsibilities. This "team" approach, which may involve social workers, transplant coordinators, and clergy, allows for a well-timed, sensitive inquiry and avoids family perceptions of conflict of interest that may occur when a request is made by the physician who also renders definitive care.

In many patients with lethal head injuries, severe physiologic derangements develop both before and after brain death occurs. The loss of autonomic control and central hypotension (65% of patients), neurogenic pulmonary edema (52%), diffuse coagulopathy or disseminated intravascular coagulation (42%), hypothermia (41%), and massive diuresis (diabetes insipidus) (38%) all may contribute to the reported 15% to 30% incidence of cardiopulmonary death before organ recovery. Despite the severity of abnormalities in these patients, a 77% two-year survival rate for transplanted kidneys, and the excellent results obtained with cardiac transplants support an aggressive approach to physiologic maintenance. The commitment of personnel and resources to the physiologic support of this group of organ donors must be substantial. A lack of interest and skill in managing these problems further contributes to donor organ loss.

An improvement in the current rates of organ procurement will depend on earlier identification and screening of potential donors, the establishment of standards for the monitoring and declaration of brain death, a more carefully timed and sensitive approach to next-of-kin requests, the anticipation and treatment of common donor physiologic derangements, and the education of the lay public and medical professionals regarding the benefits and practice of donating organs.

The time, energy, and knowledge base required to expedite organ procurement usually exceed those of individual treating physicians. Organ procurement agencies were developed in part to help facilitate this process. Legislation passed by Congress in 1986 allowed further restructuring and expansion of regional organ procurement agencies operating either within or independently of hospital systems. Once contacted, organ procurement agencies provide donor eligibility information and medical and immunologic screening and may, if invited, assist the treating physician with obtaining consent and the physiologic support of eligible donors. It should be the responsibility of every physician caring for patients with anticipated fatal neurologic injuries or disease to contact the regional organ procurement agency for information and guidance regarding the procedure for organ donation.

ROBERT C. MACKERSIE, MD
San Diego, California

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Surgical Treatment of Chronic Ulcerative Colitis

CHRONIC ULCERATIVE COLITIS with its attendant symptoms and risk of malignant degeneration can be cured by proctocolectomy. A reluctance to accept a permanent ileostomy, however, has often prevented a surgical cure, occasionally with tragic results. The development of continent ileostomy and restorative proctocolectomy—ileal pouch-anal anastomosis—has shifted the balance toward the acceptance of earlier surgical treatment. In recent years, results of these complex operations have improved considerably.

Proctocolectomy with Brooke ileostomy remains the standard against which other operations for chronic ulcerative colitis are measured, though it is the option least commonly chosen by patients. A subtotal colectomy with ileoproctostomy remains a reasonable option in selected patients. Although it does not eliminate the risk of cancer or inflammation in the remaining rectal mucosa, subtotal colectomy does provide excellent functional results with low morbidity. Its use should be considered in patients with marginal sphincter function, an uncertain diagnosis, or advanced cancer. The incidence of cancer in the preserved rectum is about 6%, and rectal removal for recurrent inflammation is necessary in 10% to 15%. The Kock pouch is the most technically demanding option and has the greatest complication rate. Recent modifications in the construction of the nipple valve have greatly reduced the need for late reoperation. The Kock pouch offers advantages to patients who decline the Brooke ileostomy and whose life-style does not allow them ready access to toilet facilities.

The most commonly chosen operation is restorative proctocolectomy. In this procedure, all colonic and rectal mucosa is removed, although a short segment of rectal muscle stripped of its mucosa may be left in place. A reservoir (pouch) created from terminal ileum is then anastomosed in the anal mucosa. Restorative proctocolectomy was first performed in 1978, and long-term outcome data are now becoming available. The operative mortality of the procedure approaches zero, and the incidence of pelvic sepsis should be less than 5%. The most common cause for reoperation remains small bowel obstruction. Patients who undergo restorative proctocolectomy can expect to have five to six bowel movements per 24-hour period, including one movement at night. Most patients (95%) have satisfactory daytime continence, although about 20% will have nocturnal soiling. Pouchitis, nonspecific inflammation of the reservoir, occurs

in 10% to 20% of patients. Pouch function improves over the first 18 months after the operation, and about 90% of patients are able to return to work.

In all studies of long-term outcome, operative complications diminish and the functional results improve with experience. This reflects both a learning curve for this complex operation and the effect of the technical refinement of the procedure. The following lessons were learned from the early experience:

- Preserving a short rectal muscular cuff of about 2 cm diminishes the risk of postoperative complications. A lengthy mucosectomy, which is associated with the long-term impairment of anal sphincter function, is therefore unnecessary.
- Using the shortest possible efferent limb prevents problems with pouch emptying.
- Bladder and sexual function is best preserved with the use of a perimuscular dissection technique (pelvic dissection proceeds anterior to the superior rectal artery).
- Restorative proctocolectomy may be done safely in selected patients without a protecting ileostomy. Because of the profound consequences of postoperative pelvic sepsis, however, many surgeons continue to routinely use a temporary ileostomy.
- Many malfunctioning pelvic pouches may be salvaged through a remedial operation.
- No specific pouch design—J versus S versus W and so forth—appears to be consistently superior.

Despite considerable limitations, restorative proctocolectomy has made surgical cure acceptable to a large number of patients with chronic ulcerative colitis. Lessons learned in the past 13 years have substantially improved the likelihood of a successful outcome.

JAMES STONE, MD
Stanford, California

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Efficacy of Carotid Endarterectomy in Randomized Trials

CAROTID ENDARTERECTOMY is designed to reduce the risk of stroke in patients with extracranial cerebrovascular disease. Its efficacy has recently been challenged on the basis that communitywide studies show operative morbidity and mortality to be unacceptably high, offsetting potential benefits. Retrospective reviews of the literature comparing the results of the operation with natural history studies show clear benefit, but such studies are subject to selection bias and are generally discounted by the scientific community. The net result of this controversy has been uncertainty in the medical community concerning referring patients for the operation. If the operation is of value, it is being withheld from patients who may benefit. If it is not of value, then it is being done in patients who may suffer surgical consequences without deriving benefit.

Efforts are now under way to answer the clinical questions concerning efficacy. The Department of Veterans Affairs and the National Institutes of Health (NIH) are sponsoring separate prospective randomized trials in patients with symptomatic and asymptomatic carotid stenoses. The VA asymptomatic study will be completed shortly, and the NIH asymptomatic trial is well under way.

The value of the prospective randomized trial was recently highlighted by a "clinical alert" issued by the NIH on February 25, 1991, concerning the North American Symptomatic Carotid Endarterectomy Trial. This multi-institutional study was begun about three years ago to determine if symptomatic patients (those with transient ischemic attacks or previous mild stroke) with ipsilateral carotid stenosis (30% to 99%) will have fewer fatal and nonfatal strokes after a carotid endarterectomy than patients treated with medical management, including the use of aspirin, alone. The NIH stopped the portion of the trial dealing with high-grade stenoses (70% to 99%) after only 18 months because surgical treatment was found to be so efficacious that a statistically significant end point was reached. The operation reduced the risk of stroke by 71% and that of death by 58% when compared with medical management, including aspirin antiplatelet therapy. The NIH recommended that patients with symptomatic carotid stenoses in the 70% to 99% range who are acceptable risks for the operation be treated with carotid endarterectomy. Implicit in this recommendation is that the operation be carried out by competent surgeons whose morbidity and mortality rate for stroke is less than 5%. The net result of this study is that a definitive answer has been reached, and the debate concerning the efficacy of carotid endarterectomy for symptomatic high-grade stenosis is put to rest.

If the medical profession will support the trials of asymptomatic carotid stenosis and symptomatic low-grade stenosis (30% to 69%) by referring patients to participating centers, a definitive answer in the remaining patient categories will be forthcoming.

WESLEY S. MOORE, MD
Los Angeles, California

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Surgical Treatment of Hemoptysis

BRONCHITIS IS THE MOST common single cause of bronchial bleeding. Massive hemoptysis, frequently defined as 600 ml of bleeding or more in 48 hours, is caused about 60% of the time by inflammatory lesions. Tuberculosis, bronchiectasis, lung abscess, fungus infection, and pneumonia are likely causes of massive bleeding. Less than 10% of cases of massive hemoptysis are the result of bronchogenic carcinomas because lung cancer that bleeds usually produces blood-streaked sputum. Carcinoid tumors are uncommon, but they are important considerations when hemoptysis occurs because they may be invisible with plain chest radiographs or computed tomographic scans. These endobronchial or endo-

tracheal neoplasms, recently referred to as neuroendocrine tumors, are Kulchitsky's cell carcinomas. Bronchitis alone may cause hemoptysis.

The most important diagnostic test for evaluating bronchial bleeding is bronchoscopy, and this should be done in every patient with hemoptysis. A chest x-ray film alone is usually insufficient to evaluate the cause of bronchial bleeding. A complete evaluation, including radiographs, computed tomographic scans, sputum cytologic study, and cultures may fail to yield a specific diagnosis. To establish the site of origin and the presence or absence of an endobronchial neoplasm, bronchoscopy should be done while bleeding is active. With few if any exceptions, biopsies of tumors can be safely done. If there is fear of massive hemorrhage as a result, bronchoscopy should be done where the examination can be immediately changed from one using a flexible instrument to the use of a rigid bronchoscope under general anesthesia.

If potentially life-threatening hemorrhage occurs during bronchoscopy, large tube access to the airway must be maintained. A rigid bronchoscope with ventilation attachment should be advanced into the main-stem bronchus of the lung that is not bleeding, or a bronchial blocking balloon can be advanced under direct vision into the main stem of the bronchus of the bleeding lung. Flexible bronchoscopes become nearly useless in the presence of massive hemoptysis because their suction channels are too small to maintain visibility of the tracheobronchial tree. Adequate ventilation of the nonbleeding lung is essential. The topical use of epinephrine and tamponade at the bleeding site usually suffice to arrest the hemorrhage. In rare cases, it is necessary to proceed with emergency thoracotomy, leaving the flexible bronchoscope or bronchial blocking balloon in place to protect the aerating lung. The use of divided endotracheal tubes of the Carlens type is not recommended because such tubes have small lumens that easily plug with clot and the correct placement under emergency conditions is usually difficult and hazardous.

In most instances, there is time to attempt the nonoperative control of massive hemoptysis. Bronchial arteriography with embolization is useful and should be done if bleeding has been 100 ml or more or if lesser bleeding has been recurrent. After localization of the bleeding bronchial artery, an absorbable gelatin sponge (Gelfoam), polyvinyl alcohol, or Gianturo coils are inserted into the bleeding vessel. The most serious complication of bronchial embolization is an unintentional distal embolization that may cause paraplegia from infarction of a portion of the spinal cord. Embolization of the bronchial arteries for the control of hemorrhage has been effective in more than 90% of patients, but there has been a rebleeding rate of about 15%.

Bronchial bleeding from inflammatory causes that may be arrested or cured with nonoperative therapy should be treated with appropriate medications. The definitive treatment of hemoptysis from endobronchial neoplasms or massive bleeding from inflammatory sites requires resection of the source of the hemorrhage.

Thoracotomy is indicated as the primary treatment of massive hemoptysis if bronchoscopy has revealed a readily curable localized endobronchial lesion, such as carcinoid or stage I carcinoma. Otherwise, an operation is necessary if there is persistent bleeding after unsuccessful embolization. Lobectomy is usually required, but segmentectomy may suffice. If bleeding stops temporarily, and a semielective operation can be planned, a parenchyma-preserving bronchial sleeve resection may be possible.

JOHN R. BENFIELD, MD
Sacramento, California

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Laparoscopic Cholecystectomy

THE RECENT DEVELOPMENT of less invasive alternatives to traditional cholecystectomy has stimulated the modernization of the surgical treatment of cholelithiasis. While oral dissolution therapy, extracorporeal lithotripsy, endoscopic stone extraction, percutaneous stone extraction, and contact dissolution all have legitimate roles in selected patients, only surgical removal of the gallbladder ensures long-term freedom from recurrence without the risk, cost, and inconvenience of continuous or repeated treatment. Laparoscopic cholecystectomy, because of its minimal trauma to the abdominal wall, offers all of the therapeutic advantages of traditional open cholecystectomy without the morbidity and prolonged disability attending laparotomy.

The tangible benefits of laparoscopic cholecystectomy include minimal postoperative pain and ventilatory compromise, a short hospital stay, a rapid resumption of normal activity, minimal scarring, and reduced cost. Over the past two years, the operation has achieved enormous popularity among surgeons and patients and has replaced open cholecystectomy as the preferred procedure for symptomatic cholelithiasis.

While laparoscopic cholecystectomy has already established itself as a legitimate advance in biliary surgical technique, its indications are still evolving and its mortality and serious morbidity rates suggest that further study is needed. The procedure is ideally suited to patients in need of elective treatment of symptomatic uncomplicated cholelithiasis. It is contraindicated in those with acute cholangitis, acute pancreatitis, perforated cholecystitis with diffuse peritonitis, portal hypertension, severe coagulopathy, or morbid obesity. Acute cholecystitis, choledocholithiasis, previous upper abdominal operation, and pregnancy are relative contraindications but have not deterred aggressive and experienced laparoscopic surgeons. Routine intraoperative cystic duct cholangiography is done to discover unsuspected common bile duct stones and delineate the biliary anatomy so as to minimize iatrogenic injuries to the extrahepatic ductal system.

With more than 3,000 cases reported, there have been less than a 0.1% perioperative mortality, a 3% major complication rate, and less than a 1% ductal injury rate. Several major centers, however, are now having a pronounced increase in the referral of patients with iatrogenic bile duct injuries. Clearly there is a steep learning curve with the new technique, and most technical errors occur during a surgeon's first 50 cases. A number of injuries have been associated with the use of laser dissection. It is becoming apparent that current laser technology offers no real advantage over electrocautery but adds substantially to the cost.

More than 500,000 cholecystectomies are done each year in the United States, and it is estimated that three fourths of these are amenable to the laparoscopic technique. The average hospital length of stay is one day for the new procedure compared with three to five days for standard open cholecystectomy. The time to full recovery and return to work is similarly reduced to one to two weeks from four to six weeks. This represents an enormous advance in surgical care for a large group of patients typically at the height of their productivity.

There is universal agreement that laparoscopic cholecystectomy is here to stay. The incidence and consequences of extrahepatic bile duct injury need to be analyzed critically. Proper training, credentialing, proctoring, and privileging will minimize this dreaded complication. To ensure maximum patient safety, it is imperative that only fully qualified general surgeons with formal instruction and animal laboratory experience be allowed first to assist at and then to do laparoscopic cholecystectomy.

BRUCE E. STABILE, MD
San Diego, California

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Alerts, Notices, and Case Reports

Fulminant Hepatic Failure Following Low-Dose Sustained-Release Niacin Therapy in Hospital

DAVID J. FISCHER, MD
LAWRENCE L. KNIGHT, MD
ROBERT E. VESTAL, MD
Boise, Idaho

NIACIN HAS GAINED wide use as an effective, relatively inexpensive therapy for hypercholesterolemia. Toxic hepatitis due to the use of this drug is rare, poorly understood, and observed more frequently with higher doses (more than 3 grams daily).[1] Sustained-release preparations have gained popularity because of less discomfort from flushing and pruritus. Unfortunately, their use has been associated with increased hepatotoxicity.[1-3] Heightened vulnerability of the liver to the effects of sustained-release (SR) niacin associated with illness or other medications has not been reported. We report the case of a patient, admitted to hospital for a respiratory illness, in whom unexplained fulminant hepatic failure developed following treatment with 2 grams a day of niacin. Although niacin-induced hepatic toxicity is well described, this is the first report of a fatality associated with low-dose SR niacin therapy.

Report of a Case

The patient, a 56-year-old man with emphysema, started taking SR niacin (United Research Laboratories, Philadelphia, Pa), 250 mg twice a day, in January 1989 for the treatment of hypercholesterolemia (7.11 mmol per liter [275 mg per dl]) after dietary modifications had failed. His dose was increased in June 1989 to 1 gram twice a day. The values of serum aspartate aminotransferase (AST) and alkaline phosphatase were normal before he began taking SR niacin, and there was no previous history of infectious hepatitis, jaundice, blood transfusions, substantial alcohol use, known exposure to hepatotoxins, or the use of illicit drugs.

He was admitted to the hospital in October 1989 for the treatment of bronchospasm with cough and hypoxia due to an upper respiratory tract infection and possible pneumonia. He did not have abdominal pain, nausea, or vomiting. In addition to niacin, his medications before admission were metaproterenol sulfate and triamcinolone acetonide inhalers for bronchospasm and clotrimazole and hydrocortisone 1% creams for a chronic rash on his hands and legs. Although he said that he was taking the niacin as prescribed (1 gram twice a day), later review of his unused medications indicated that he may have been taking only half of the prescribed dosage.

On physical examination, the patient was afebrile and had mild tachypnea with decreased breath sounds. An abdominal examination revealed no tenderness or organomegaly. Laboratory values were notable for the following: leukocyte count 9.0×10^9 per liter, hemoglobin 140 grams per liter, PaO_2 40.5 mm of mercury, cholesterol 4.74 mmol per liter (183 mg per dl), and normal electrolytes. Liver function tests were not done on his admission to the hospital. Methylprednisolone sodium succinate, a combination of ampicillin sodium and sulbactam sodium, sucralfate, and heparin prophylaxis were added to his regimen of bronchodilators and SR niacin, 2 grams daily.

The patient's respiratory symptoms waxed and waned over the first five hospital days with gradual improvement in oxygenation and normal oral food intake. On the fifth hospital day, he complained of burning epigastric pain. On rectal examination, his stool was guaiac-positive. Steroid therapy was discontinued, and ranitidine was added. On the sixth hospital day, icterus, right upper quadrant pain, and emesis developed. Oral medication therapy including niacin was discontinued. On the seventh hospital day, liver function test results were abnormal, with an alkaline phosphatase level of 4.5 μmol per liter (270 units per liter), bilirubin 103 μmol per liter (6.0 mg per dl), aspartate aminotransferase (AST)

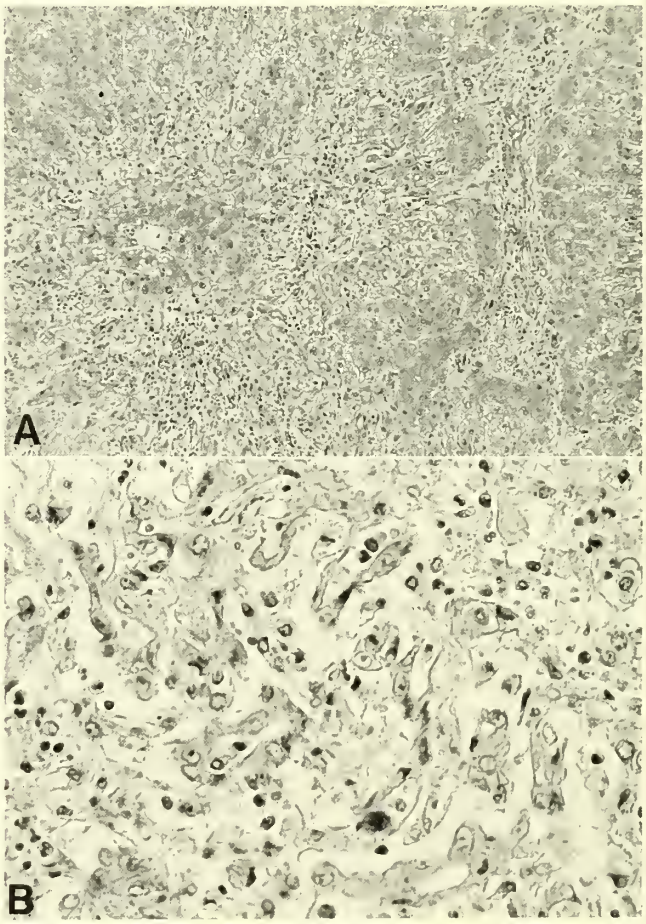

Figure 1.—**A,** Hepatic damage is most severe through the midzonal area, where necrotic hepatocytes are intermingled with neutrophils and macrophages. Damage is most severe through paracentral and midzonal areas. Small zones of less altered parenchyma occupy a periportal location (original magnification × 100). **B,** A higher power (× 400) view shows extensive vacuolization of hepatocytes.

(Fischer DJ, Knight LL, Vestal RE: Fulminant hepatic failure following low-dose sustained-release niacin therapy in hospital. West J Med 1991 Oct; 155:410-412)

From the Medical (Drs Fischer and Vestal) and Laboratory (Dr Knight) Services and the Clinical Pharmacology and Gerontology Research Unit (Dr Vestal), Veterans Affairs Medical Center, Boise, Idaho, and the Departments of Medicine (Drs Fischer and Vestal), Pharmacology (Dr Vestal), and Pathology (Dr Knight), University of Washington School of Medicine, Seattle.

Reprint requests to Robert E. Vestal, MD, Clinical Pharmacology and Gerontology Research Unit (151), VA Medical Center, 500 Fort St, Boise, ID 83702.

ABBREVIATIONS USED IN TEXT

ALT = alanine aminotransferase
AST = aspartate aminotransferase
SR = sustained release

10.90 μkat per liter (654 units per liter), and alanine aminotransferase (ALT) 13.90 μkat per liter (834 units per liter). Abdominal ultrasonography and abdominal computed tomography revealed no obstruction of the biliary architecture and no parenchymal abnormalities. On the eighth hospital day, a coagulopathy and stage I encephalopathy developed with liver enzyme levels peaking at an AST of 33.5 μkat per liter (2,010 units per liter) and an ALT of 42.8 μkat per liter (2,567 units per liter). Tests for hepatitis A antibody (immunoglobulin M) and hepatitis B surface antigen were negative. The patient's clinical condition deteriorated rapidly, with worsening encephalopathy and the development of upper gastrointestinal bleeding. Transplantation was considered but not pursued because of severe underlying emphysema—a forced expiratory volume in one second of 0.51 liters versus a forced vital capacity of 1.7 liters. He was vigorously treated in the intensive care unit with lactulose, fresh frozen plasma, packed erythrocytes, and cryoprecipitate. On the tenth hospital day, the patient died.

An autopsy confirmed the underlying clinical diagnosis of chronic pulmonary emphysema. Coronary and aortic arteriosclerosis and diverticulosis coli were noted. There were ascites, peripheral edema, and pulmonary hyperemia with bilateral pleural effusion. Pneumonic consolidation, infarction, or tumors were not observed. Superficial erosions were noted on examination of the gastric mucosa. The liver weighed 1,000 grams. Cystic and common bile ducts were patent and of normal caliber. On microscopic examination of sections of liver, there was acute hepatic necrosis with prominent fine vacuolization of hepatocytes accompanied by bile stasis. There were some areas of preserved lobular architecture and other areas of complete lobular devastation (Figure 1). Damage was most severe in the paracentral and midzonal areas.

Discussion

The admission history and physical examination and the subsequent hospital course suggest that the hepatotoxic insult occurred after admission to the hospital. Medications other than niacin could have contributed, but there are no specific reports linking methylprednisolone, ampicillin-sulbactam, sucralfate, or heparin to severe hepatotoxicity. Although ranitidine use rarely causes liver injury, it is an unlikely cause in view of the appearance of jaundice the day after ranitidine therapy was begun. Infectious causes including hepatitis B or C are also possible, but hepatitis A and B serologic tests were negative. Although a serologic test for hepatitis C was not available at the time of this patient's admission to hospital, he had no risk factors for hepatitis C. There was also no history of alcohol abuse. Furthermore, the liver did not have the pattern of viral hepatitis or alcohol-induced hepatitis. Its histologic features were typical of niacin-induced hepatic injury.[4] A unique histologic feature in this patient is the paracentral and midzonal localization of the liver injury. This was not noted in a previous report of fulminant hepatic failure.[1] The patient did not receive acetaminophen, and other hepatotoxins are unlikely in the supervised environment of the hospital. Finally, the patient did not have clinical evidence of heart failure or hypotension as a cause for ischemic hepatitis.

The actions of niacin on the liver resulting in decreased cholesterol and triglyceride levels are not understood, nor is the mechanism of hepatotoxicity. Although reports of hepatotoxicity induced by niacin use have appeared sporadically since 1959, with increased enthusiasm for lipoprotein modification, the use of niacin has increased along with reports of toxicity. Most reported cases involve hypercholesterolemic patients treated with crystalline niacin in doses of 4 to 4.5 grams daily, usually for several months.[5] In these reports, the clinical picture was typical of hepatitis with jaundice, pruritus, malaise, hepatomegaly, and mild to moderate elevations of serum bilirubin, alkaline phosphatase, and aminotransferase levels. After the withdrawal of niacin, symptoms usually resolved within a week and biochemical abnormalities resolved within a month. The histologic changes of acute toxic effects are also reversible as occurred in a patient taking 4.5 grams of niacin per day whose hepatitis recurred after rechallenge. The initial liver biopsy showed both massive and submassive lobular collapse, increased fibrosis in some areas of collapse, pronounced cholestasis with canalicular bile plugging, and vacuolated cytoplasm in many hepatocytes.[5] A second liver biopsy done 14 months after the initial one revealed normal architecture.

Although SR niacin is generally thought to be more hepatotoxic than crystalline preparations, it is unknown whether the increased toxicity is due to different local effects on liver cells, a longer exposure time with higher local concentrations, or different absorption characteristics. Three patients who had previous SR niacin-induced hepatitis with equal or higher doses of crystalline niacin reported no evidence of recurring hepatocellular damage, suggesting that the effects of these two preparations may differ substantially.[3] Our patient received SR niacin capsules containing coated pellets that release niacin at progressively longer intervals, depending on the thickness of the coating. It is not known whether a constituent of the SR formulation contributes to the liver injury.

Fulminant hepatic failure associated with SR niacin is poorly characterized and can occur in a variety of clinical circumstances. Mullin and co-workers described the case of a patient who tolerated 6 grams of crystalline niacin daily but in whom fulminant hepatic failure developed three days after an unintentional switch to an SR preparation; the patient required liver transplantation.[1] Hodis recently reported fulminant hepatic failure in an otherwise healthy 32-year-old patient taking 500 mg of SR niacin daily for eight weeks.[6] This patient survived hepatic coma. Our patient had tolerated SR niacin use for four months before admission, with the occurrence of fatal hepatic failure seven days after an increase in dosage from 1 gram to 2 grams daily (assuming he was taking only half of his prescribed dose at home). Whether his acute respiratory illness or other unidentified aspects of his hospital care contributed to the severity of his hepatic failure is unclear.

These recent reports emphasize the need for clinicians to remain alert to the possibility of serious liver dysfunction in any patient taking niacin. Our experience suggests that patients admitted to hospital for any reason who take niacin should be questioned regarding current usage and observed closely for liver function abnormalities or gastrointestinal

complaints. In addition, because SR niacin may be more hepatotoxic in certain patients, its use probably should be restricted to those patients who cannot tolerate the side effects from crystalline niacin formulations.

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Gastric Tuberculosis Presenting as Fever of Unknown Origin

SHELLEY R. SALPETER, MD
San Jose, California

RICHARD M. SHAPIRO, MD
JOHN D. GASMAN, MD
Stanford, California

While the incidence of pulmonary tuberculosis has been gradually declining over the past 50 years, that of extrapulmonary tuberculosis has remained relatively constant, and it accounts for almost 20% of all tuberculosis cases.[1,2] Clinically evident tuberculosis of the stomach is rare and is usually associated with concurrent lung infection.[3,4] Cases of isolated gastric tuberculosis without evidence of pulmonary involvement have been reported sporadically.[4] An awareness of these atypical presentations of tuberculosis is necessary for the proper diagnosis and prompt institution of therapy.[5,6] Herein we describe a case of a 74-year-old man with isolated gastric tuberculosis who presented with fever of unknown origin and weight loss. We take this opportunity to review the literature on this disorder, making particular reference to the case discussed here.

Report of a Case

The patient, a 74-year-old man from Nicaragua, was admitted for the evaluation of daily spiking fevers, epigastric pain, and a 9-kg weight loss over the previous three months. He did not have cough, shortness of breath, or a change in bowel habits. The patient had been healthy previously and denied any knowledge of previous tuberculin skin tests. He was married with a single sexual partner and had emigrated from Nicaragua 30 years ago. He had not traveled recently. On admission he was afebrile with normal vital signs. There was no palpable lymphadenopathy, the findings of a cardiac examination were benign, and his lungs were clear. The abdomen was soft with mild epigastric tenderness, and there was no hepatosplenomegaly. An examination of the stool was negative for occult blood. Laboratory values were as follows: urinalysis normal, hematocrit 0.31 (31%), and leukocyte count 13×10^9 per liter (13,000 per μl) with 0.62 (62%) neutrophils, 0.23 (23%) band forms, and 0.06 (6%) lymphocytes. The erythrocyte sedimentation rate (Westergren) was 118 mm per hour. Alkaline phosphatase was 147 U per liter, alanine aminotransferase 31 U per liter, aspartate aminotransferase 41 U per liter, and γ-glutamyl transferase 441 U per liter. A chest radiograph was normal.

During his hospital stay, the patient continued to have daily fevers, with temperatures exceeding 38.5° C (101.3° F) despite antipyretic therapy. The evaluation included multiple cultures of blood, sputum, urine, and stool specimens, all of which were negative for pathogens. An intermediate tuberculin skin test was positive with 15 mm of induration. A bone marrow biopsy was normal, and a liver biopsy revealed nonspecific acute and chronic inflammation. Cultures of bone marrow and liver were negative for bacteria, fungi, and mycobacteria. A computed tomographic (CT) scan of the chest and abdomen revealed a 4- by 4- by 3-cm submucosal mass at the gastroesophageal junction. A mucosal biopsy of the gastric mass revealed acute and chronic gastritis. A second biopsy showed submucosal ulceration and necrotizing granulomas adjacent to lymphoid follicles with germinal center formation. Stains for fungi and acid-fast bacilli were negative.

Antituberculous therapy with isoniazid, rifampin, and pyrazinamide was begun, and the patient was discharged for outpatient follow-up. Cultures of the gastric mass subsequently grew *Mycobacterium tuberculosis* sensitive to isoniazid and rifampin. Two weeks after therapy was initiated, he was completely afebrile. After one month his epigastric pain had resolved and he had gained 7 kg. A CT scan at the time showed notable diminution in the size of the gastric mass to 2.5 by 2 by 2 cm. Another scan at three months showed a residual 1- by 1-cm thickening at the gastroesophageal junction.

Discussion

In the early 1900s, tuberculous involvement of the gastrointestinal tract due to pulmonary tuberculosis was a fairly common occurrence, especially in patients with far-advanced lung infection.[7,8] After the introduction of successful antituberculous regimens, the percentage of pulmonary tuberculosis cases with clinically evident secondary gastrointestinal involvement decreased from 38% to less than 5%.[7,9]

Gastrointestinal tuberculosis can occur in the absence of additional sites of infection. In the first half of the century, this form of the disease was due mainly to the ingestion of *Mycobacterium bovis* in infected milk. Bovine intestinal tuberculosis has now been essentially eradicated in countries with milk pasteurization and tuberculous testing of dairy herds.[7,8] Isolated gastrointestinal infection with *M tuberculosis*, however, remains a problem today, representing about 3% of all cases of tuberculosis and at least 50% of all cases of gastrointestinal tuberculosis.[7,8,10,11] Its incidence may actually be rising in recent years, especially in populations with immigrants from Third World countries and patients with the acquired immunodeficiency syndrome.[2,10-13] Only about 50% of these cases are diagnosed accurately, mainly because tuberculosis is often not considered in the diagnosis.[14]

There has been much debate regarding the origin of gas-

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From the Department of Medicine, Stanford University Medical Center, Stanford, California. Dr Salpeter is now with the Santa Clara Valley Medical Center, San Jose, California

Reprint requests to Shelley R. Salpeter, MD, Valley Health Center, 750 S Bascom Ave, Rm 320, San Jose, CA 95128.

trointestinal infection with *M tuberculosis*. The three main proposed routes that may all play a part are direct ingestion, hematogenous spread, and lymphatic spread. Lymphatic spread would occur by transluminal transport of the tubercle bacillus to the submucosal lymph nodes with subsequent colonization and the formation of granulomas.[7,8,12,15] This theory is supported by the fact that most cases of gastrointestinal tuberculosis occur in areas rich in lymphatics, such as the ileocecal region.[7,9] Our case appears to substantiate this theory because the submucosal gastric biopsy specimen contained lymphoid follicles with germinal centers adjacent to the granulomas. It is interesting to note that often gastrointestinal tuberculosis develops in immigrants, like the patient presented here, several years after they leave their country.[12,13,16] It has been hypothesized that the infection remains dormant in the mesenteric lymph nodes with reactivation and spread at a later date.[12]

Tuberculous involvement of the stomach has been reported to occur in 0.5% to 3% of all cases of gastrointestinal tuberculosis and is often due to pulmonary infection.[9,12,13,17] Isolated gastric tuberculosis is even rarer, with to our knowledge only ten other cases having been reported in the English-language literature over the past decade.[4,5,11-13,15,17-19] As with other forms of isolated gastrointestinal tuberculosis, its incidence is probably increasing. As the case we describe here typifies, there is no pathognomonic clinical feature. Common symptoms include fatigue, weight loss, fever, and abdominal pain.[3] Laboratory findings are equally nonspecific and can show anemia and an elevated sedimentation rate.[13,14] Tuberculin skin tests are positive in about 65% of cases.[2,13] Radiographic studies may show an ulcer or a submucosal mass, most commonly in the antrum or pylorus.[3,4] Lesions may be ulcerative, hypertrophic, or a combination of the two, called ulcerohypertrophic.[3,4,7] On endoscopic or surgical biopsy, granulomas are generally present in the submucosa and subserosa, with a nonspecific inflammatory reaction in the mucosa.[7] The clinical diagnosis is often aided by the presence of caseation necrosis in the granulomas, but a definitive diagnosis usually requires the histologic or bacteriologic identification of *M tuberculosis*.[13,16] Early articles suggested that 10% of cases of gastric tuberculosis were associated with gastric carcinoma, but this correlation has not been verified in recent data.[19]

The treatment of gastric tuberculosis is similar to that of pulmonary tuberculosis.[20] Short-course treatment (six or nine months) appears to be effective, with a rapid resolution usually seen in symptoms, fevers, and the size of the gastric mass or ulcer.[19,21,22] Early suggestions that surgical extirpation of the gastric lesions is essential for cure are no longer substantiated, unless acute complications are present.[5,10,19,20] The patient in this case had a dramatic response to antituberculous treatment alone, with complete resolution of his fevers within two weeks and a rapid diminution in the size of his gastric mass.

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Mouse Joint—Another Manifestation of an Occupational Epidemic?

LEE A. NORMAN, MD, MHS
Seattle, Washington

It is an occupational epidemic that goes by many names: repetitive strain injury, overuse syndrome, or, because it usually affects the shoulder, arm, wrist, and hand, it has been called the chronic upper limb pain syndrome. Although not new, having been accurately described by Velpeau in 1840,[1(p94)] repetitive strain injuries have increasingly been recognized in the past one to two decades. There are skeptics who believe that generous workers' compensation systems and the social acceptability of repetitive strain injuries have fostered the emergence of the epidemic, both in the United States and worldwide (J. Kavanaugh, "Keyboard Cripples: The Avalanche Looms," *Business Review Week*, November 17-23, 1984, pp 37-52).[2] Indeed, studies that attempt to systematically categorize diagnoses of these injuries show that, in most instances, specific and accurate clinical diagnoses are not made.[3,4] Miller and Topliss reported that in 229 patients with repetitive trauma, 200 were given the diagnosis of chronic upper limb pain syndrome and that only 29 had specific soft tissue or rheumatologic disorders identified[5]: fibrositis (15), rotator cuff syndrome (3), mild rheumatoid arthritis (3), cervical referred pain (3), lateral epicondylitis (2), de Quervain's tenosynovitis (1), carpal tunnel syndrome

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From the Family Practice Residency Program, Swedish Hospital Medical Center, and the Department of Family Medicine, University of Washington School of Medicine, Seattle.

Reprint requests to Lee A. Norman, MD, MHS, Associate Medical Director, Swedish Hospital Family Practice Residency Program, 700 Minor Ave, Seattle, WA 98104.

(1), and psoriatic arthritis (1). The authors pointed out that these 29 patients should likely not have been given the diagnosis of repetitive strain injury in the first place.

Overuse syndromes and repetitive strain injuries are associated with many different kinds of activities including athletics,[5-8] sign language interpreting for the deaf,[9] the use of musical instruments[10-13] and video games,[14] and many different employment and occupational settings.[15,16] Carpal tunnel syndrome is the most commonly recognized specific repetitive strain injury. The State of Washington Department of Labor and Industries estimates that symptoms of carpal tunnel syndrome will develop in 10% of all employed adults in Washington sometime during their employment careers. The great variety of overuse syndromes has produced colorful-sounding names: Nintendo neck,[14] guitar nipple,[17] cello scrotum,[18] and potato harvester's foot drop.[19] That the names for the disorders are interesting, however, should not trivialize their importance. Many result in patient discomfort and loss of work productivity, especially when the mechanism of injury is unknown or when the offending causative agent is widespread in our society, as described in the following case.

Report of a Case

The patient, a 40-year-old left-handed man, saw his physician because of dull, persistent aching pain in the area of his second and third metacarpophalangeal joints of his right hand. The patient, an accountant, said the pain had been gradually increasing for two or three months. It was not associated with trauma, new activity, or underlying bone or joint disease. Gripping made the pain worse, and he had noticed decreased strength in the hand. He had no other painful or swollen joints or medical problems.

Examination of his hand showed tenderness and mild swelling at the base of his second and third fingers, worse on the palmar side than on the dorsum. There were no nodules, the flexor tendons were not thickened, the skin showed no erythema, and there was no joint effusion or motion limitation.

The patient was diagnosed as having flexor tendinitis and was treated with a regimen of ibuprofen, rest, and a splinting device. His symptoms resolved within four weeks. He later returned with a recurrence of his symptoms, adding that his wife had the same problem develop in the same area of her right hand. Additional history obtained at that time made the diagnosis obvious. It has remained a problem for him, though, because of his unwillingness to change his computer equipment at work.

Discussion

The patient and his wife were suffering from a heretofore-unreported condition: mouse joint. They both extensively used personal computers at work and at home that were equipped with mouse operating devices. The hand pain was likely the result of repetitive flexion activity of the index and middle fingers as required for mouse operation. "Mouse joint," it is emphasized, should not be confused with "joint mouse," the commonly used orthopedic and radiologic term that describes the small fibrous or cartilaginous loose bodies found in synovial cavities.

The mechanism of injury for mouse joint is assumed to be like that of most overuse injuries: repetitive use with resultant microtrauma and the accumulation of metabolic products causing local inflammation, an inhibition of function, and pain. There is disagreement as to the precise terms that should be used to describe such syndromes. In the United States, England, and Scandinavian countries, inflammation is the favored cause; thus, the diagnoses "tendinitis" and "tenosynovitis" are used. In Australia, the term "repetitive strain injury" is preferred,[20] proponents citing the absence of verifiable disease in most circumstances.

Regardless of the exact cause and term, mouse joint, in this patient, exhibited many of the features of other overuse injuries: its onset was gradual, it was confined to one anatomic region, it occurred in the absence of other rheumatologic conditions, it responded to conservative treatment measures, and it recurred upon return to the offending activity. Cohn and co-workers characterized repetitive strain injury in the upper extremities of interpreters for the deaf and found that pain tended to recur after two uninterrupted hours of signing and that the average number of hours worked weekly by symptomatic interpreters was 25 hours, with a range of 9 to 40 hours per week.[9] These were not new interpreters—the average number of years worked as an interpreter was 10.8.

The treatment of all overuse injuries is essentially the same, and, except for those unusual cases that require surgical intervention where improved techniques have been developed, there has been little change through the decades. Conservative measures include rest, the use of nonsteroidal anti-inflammatory drugs, splinting, steroid injections, ice massage, physical therapy, work-site alterations, relaxation training, and the evaluation and modification of biomechanical problems.

If, indeed, repetitive strain injuries are the new "occupational epidemic," it would be beneficial to recognize the injuries early and to intervene promptly, with the hope of minimizing suffering and loss of productivity. Conversely, physicians would do well not to label a simple soft tissue complaint as an ominous-sounding repetitive strain injury if there is little to support the diagnosis and if, in so doing, they unintentionally promote incapacity in patients.

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Cisplatin Therapy-Associated Recurrent Toxic Shock Syndrome

ARNOLD C. BERMAN, MD
LAWRENCE R. BOLY, MD
San Francisco, California

THE IN VITRO RELATIONSHIP of magnesium to the production of toxic shock syndrome toxin-1 (TSST-1) has been previously described.[1-3] The in vivo relationship of systemic hypomagnesemia to the development of the toxic shock syndrome, however, has not been previously reported. We report a case of recurrent toxic shock syndrome following hypomagnesemia that was induced by cisplatin chemotherapy.

Report of a Case

The patient, a 46-year-old woman with non-insulin-dependent diabetes mellitus, presented with an acute abdomen. During an emergency laparotomy, an 11-cm ruptured "chocolate" cyst of the left ovary was found. Microscopic examination revealed a well-differentiated endometroid adenocarcinoma of the ovary. Primary uterine malignancy was excluded. The postoperative course was complicated by superficial wound infection, necessitating opening and draining.

A week later chemotherapy with cisplatin, 100 mg per m^2, and cyclophosphamide, 600 mg per m^2, was initiated. The patient felt well and was afebrile; serous discharge was noted in areas of wound separation. A wound specimen was obtained for culture.

The night the patient was discharged home from chemotherapy, fever accompanied by weakness, vomiting, and severe myalgia developed. In the emergency department, a diffuse erythematous rash was obvious. Her blood pressure was 84/50 mm of mercury in the supine position, with a pulse of 120 per minute and a temperature of 39.5°C. Conjunctivitis with purulent discharge and pharyngeal erythema with a strawberry tongue were noted. On abdominal examination, several areas of purulent wound discharge were found; otherwise, the findings were normal. Although lethargic, the patient was easily aroused and neurologic testing was normal.

Laboratory tests elicited the following values: glucose 14.9 mmol per liter (normal 3.85 to 6.05); sodium 131 mmol per liter (normal 135 to 148); potassium 3.5 mmol per liter (normal 3.5 to 5.3); chloride 100 mmol per liter (normal 98 to 106); bicarbonate 19 mmol per liter (normal 23 to 30); creatinine 100 μmol per liter (normal 53 to 124); urea nitrogen 3.2 mmol per liter (normal 2.2 to 8.2); leukocyte count 28×10^9 per liter (28,000 per μl) with neutrophils 0.69 (normal 0.40 to 0.74) and segmented forms 0.29 (normal 0 to 0.05); hemoglobin 109 grams per liter (normal 120 to 160); platelet count 377×10^9 per liter (normal 150 to 350); uric acid 330 μmol per liter (normal 140 to 355); lactate dehydrogenase 3.75 μkat per liter (normal 1.33 to 4.03); aspartate aminotransferase 0.58 μkat per liter (normal 0.084 to 0.67); alkaline phosphatase 1.5 μkat per liter (normal 0.64 to 1.93); bilirubin 18 μmol per liter (normal 1.7 to 24); total protein 65 grams per liter (normal 60 to 80); albumin 35 grams per liter (normal 32 to 50); calcium 2.17 mmol per liter (normal 2.13 to 2.55); and phosphorus 0.48 mmol per liter (normal 0.8 to 1.5). The prothrombin time was within normal limits; fibrin degradation products, negative; fibrinogen 3.2 grams per liter (normal 1.7 to 4.5). No infiltrate was seen on chest roentgenogram. Arterial blood gas determinations done with the patient receiving 4 liters of oxygen per minute by nasal cannula were pH 7.34 (normal 7.35 to 7.45); Po_2 11.2 kPa (normal 10.6 to 13.3); and Pco_2 3.8 kPa (normal 4.7 to 6.0). Abdominal wound culture done before admission was positive for *Staphylococcus aureus*. The serum magnesium level was not measured during this admission.

Initial therapy comprised fluids, pressor support, and broad-spectrum antibiotic coverage including antistaphylococcal therapy with vancomycin hydrochloride, later adjusted to nafcillin sodium according to culture sensitivity. Blood cultures were negative for pathogens, and eight days after admission the patient was discharged on a course of oral dicloxacillin sodium. On outpatient follow-up, desquamation of the palms and soles was noted. Assay of the *S aureus* from the wound specimen cultured during her hospital stay returned positive for the production of TSST-1.

Nine days after discharge, the patient returned for her second outpatient chemotherapy course of cisplatin and cyclophosphamide. She was afebrile, and her abdominal wounds were clean. The day after chemotherapy was given, the patient again presented to the emergency department with fever, rigors, myalgia, prostration, and vomiting. On examination she was febrile and hypotensive, with a generalized rash and purulent conjunctivitis. Her abdominal incision wounds had a purulent discharge.

The following laboratory values were obtained: glucose 11.4 mmol per liter, sodium 132 mmol per liter, potassium 2.8 mmol per liter, chloride 98 mmol per liter, bicarbonate 20 mmol per liter, calcium 2.02 mmol per liter, magnesium 0.37 mmol per liter (normal 0.7 to 1.0); and liver function studies normal; the leukocyte count was 27×10^9 per liter (27,000 per μl) with neutrophils 0.80 and segmented forms 0.17. A urinalysis showed trace proteinuria. Coagulation studies were normal. Gram-positive cocci were seen on a specimen taken from the wound.

Therapy with fluids, pressor support, and vancomycin was begun. Thrombocytopenia developed on the third day of her hospital stay, with a platelet count nadir of 26×10^9 per liter. Platelets were replenished before extensive surgical wound debridement, but no gross bleeding occurred and the thrombocytopenia resolved. Blood cultures were negative for pathogens, and antibiotic therapy was switched to a cephalosporin, to which the wound bacteria were sensitive. Desquamation of her palms and soles was seen after two weeks of hospital stay. Three weeks after admission, a third course of chemotherapy was administered with the patient continuing to receive oral cephalexin. Magnesium replacement was meticulously monitored. This course was uneventful.

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From the Department of Medicine, Mount Zion Hospital and Medical Center, San Francisco, California.

Reprint requests to Arnold C. Berman, MD, 235 Third Ave, Apt 1, San Francisco, CA 94118.

Discussion

The epidemiologic and clinical identification of the toxic shock syndrome according to the Centers for Disease Control rests on the following criteria[4]: Fever, rash, hypotension, and desquamation that occurs within two weeks after the disease starts must all be present. Three organ systems must be involved. Diseases that can mimic the syndrome, such as bacterial sepsis as in the case presented here, must be appropriately excluded. Clinical and laboratory manifestations of the syndrome have been recently reviewed.[5]

All four major criteria as well as evidence of multisystem involvement were met in both episodes of the toxic shock syndrome that followed chemotherapy in our patient. Cultures of blood were negative for pathogens, consistent with the diagnosis.

Renal toxicity of cisplatin has been well described,[6] along with metabolic abnormalities that include hypomagnesemia, which is common and may be profound. The hypomagnesemia is dose dependent and correlates with the cumulative cisplatin dose.[7-9] It has been reported to occur in some patients, however, after the first course of chemotherapy even with lower doses of cisplatin at 50 mg per m^2.[8,9]

Profound hypomagnesemia was documented when symptoms were present during the recurrent toxic shock syndrome episode that followed the second course of chemotherapy. Our patient received cisplatin at 100 mg per m^2, and, in addition, she had non-insulin-dependent diabetes that may have contributed to the degree of hypomagnesemia. Subclinical hypomagnesemia has been associated with poorly controlled diabetes mellitus and correlated with high levels of fasting blood glucose and an increased level of glycosylated hemoglobin.[10] The patient did not have evidence of renal disease or documented hypomagnesemia before the first course of chemotherapy, and, unfortunately, her serum magnesium level was not measured during the episode that followed the initial administration of cisplatin. The hypomagnesemia documented during the second episode required parenteral replacement.

Many studies indicate a central role for TSST-1 in the pathogenesis of the toxic shock syndrome.[11] The in vitro production of TSST-1, an exotoxin, by *S aureus* has been intensively investigated, in particular in regard to the effect of trace metals. The toxin is produced in excess in hypomagnesemic environments.[1-3]

The role of foreign bodies, particularly tampons, in menstrual toxic shock syndrome is well known.[4,5] The postulated mechanisms of tampons in the pathogenesis include a foreign body effect with alteration of the vaginal microflora[12] and the binding of magnesium by tampon fibers, producing a magnesium-deficient local environment.[3] Epidemic menstrual toxic shock syndrome was linked to the use of tampons composed of polyacrylate rayon that is thought to function as an ion exchange resin.[13]

Recurrent toxic shock syndrome in our patient was temporally related to repeated courses of chemotherapy. The symptoms occurred far too early to invoke immunosuppression by chemotherapy. Moreover, there was no evidence of leukopenia during the episodes of toxic shock.

We propose that hypomagnesemia due to cisplatin chemotherapy created conditions favorable to TSST-1 production by existing *S aureus* in the wound, precipitating the toxic shock syndrome in our patient.

We emphasize the need to monitor serum magnesium levels and to correct hypomagnesemia, if present, during episodes of this syndrome.

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Hepatocellular Carcinoma Coexisting With Hepatic Adenoma

Incidental Discovery After Long-Term Oral Contraceptive Use

JACOB KORULA, MD
ALBERT YELLIN, MD
GARY KANEL, MD
GAIL CAMPOFIORI, MD
PETER NICHOLS, MD
Los Angeles, California

THE CAUSAL RELATIONSHIP between oral contraceptive use and hepatic adenoma is well documented,[1] though the evidence for the mechanism of the transformation of adenomas to hepatocellular carcinoma is not conclusively established.[2] Recently Gyorffy and colleagues reported the development of hepatocellular carcinoma in a woman in whom hepatic adenoma was diagnosed 18 months earlier when she presented with abdominal pain.[3] We report a case where a hepatic adenoma with coexistent hepatocellular carcinoma was diagnosed in an asymptomatic woman in whom the hepatic neoplasm was identified by incidental hepatic ultrasonography.

Report of a Case

The patient, a 40-year-old woman, was referred to the University of Southern California (Los Angeles) Liver Unit

(Korula J, Yellin A, Kanel G, Campofiori G, Nichols P: Hepatocellular carcinoma coexisting with hepatic adenoma—Incidental discovery after long-term oral contraceptive use. West J Med 1991 Oct; 155:416-418)

From the Departments of Medicine (Hepatology) (Drs Korula and Campofiori), Surgery (Dr Yellin), and Pathology (Drs Kanel and Nichols), University of Southern California School of Medicine, and the USC Liver Unit, Rancho Los Amigos Medical Center (Drs Korula and Kanel), Los Angeles, California.

Reprints are not available.

for the management of a hepatic mass initially noted on ultrasonographic examination of the abdomen. She was employed, asymptomatic, and physically active at the time of referral. When she was 19, it is thought that a combination drug, ethynodiol diacetate, 1 mg, and mestranol, 0.1 mg (Ovulen 21), was prescribed for irregular menses, which she continued taking until age 28. She was briefly given a combination of norethindrone, 1 mg, and mestranol, 0.08 mg (Ortho Novum 1/80), for a few months before another combination, ethynodiol diacetate, 1 mg, and ethinyl estradiol, 35 μg (Demulen 1/35-21), was prescribed from age 28 to age 34. At that time, endometriosis was diagnosed, the oral contraceptive therapy was discontinued, and a regimen of the progestin, norethindrone acetate (Norlutate), 5 mg daily, was started. She was fairly compliant in continuing to take the prescribed medications without interruption, except perhaps for about six months before starting Norlutate therapy. She has never conceived. In March 1989, a pelvic ultrasonogram done as part of the gynecologic workup was extended to the upper abdomen, at which time a large hepatic mass was identified. She had no risks for hepatitis, history of toxin exposure, known previous liver disease, or family history of liver disease or neoplasms. Serum liver function test values, a complete blood count, and an α-fetoprotein level were in the normal range, and serologic tests for hepatitis B—hepatitis B surface antigen, hepatitis B core antibody IgG—were negative; a test for hepatitis C virus antibody was not done.

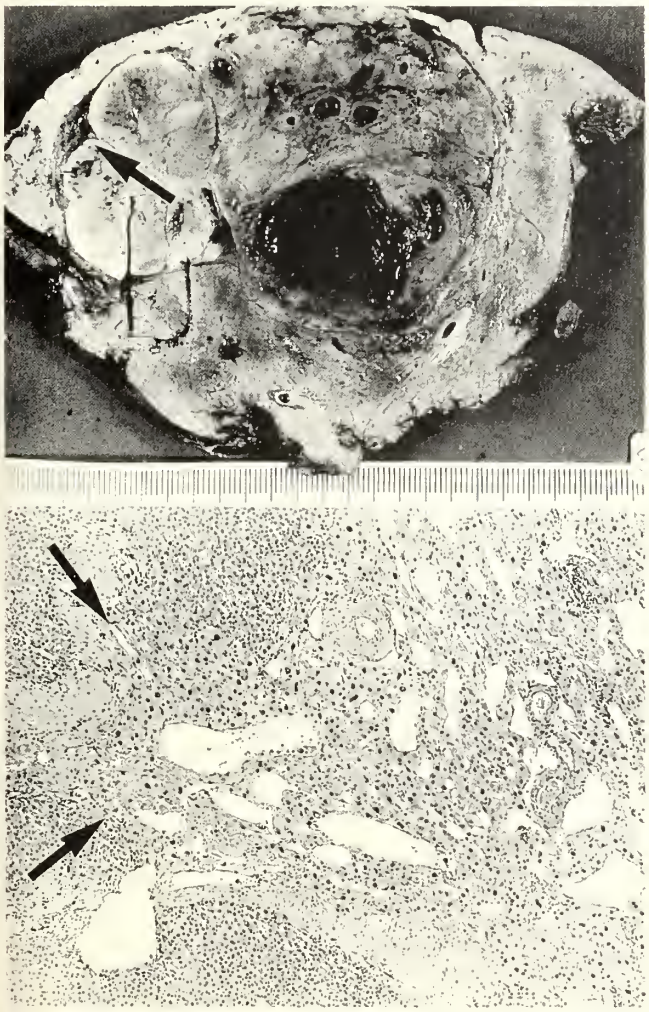

Figure 1.—Top, The photograph of a gross specimen of the resected right lobe of the liver shows the adenoma and areas of hemorrhage from the sites of needle biopsy. **Arrow** shows the focus of hepatocellular carcinoma. **Bottom,** A photomicrograph of the area indicated by the **arrow** in the gross specimen shows features of hepatocellular carcinoma with microscopic invasion into adjacent normal hepatic parenchyma **(arrows)** (hematoxylin and eosin, original magnification × 56).

A series of scanning tests ensued: computed tomography confirmed the presence of a 6.5- by 3.5-cm mass in the right lobe of the liver that corresponded with a "cold" defect on a liver scan using technetium Tc 99m sulfur colloid. A selective uptake of gallium in this "cold" defect was observed. Arteriography confirmed that it was a vascular tumor, but it showed neither the typical vascular pattern of an adenoma nor the neovascularity of hepatocellular carcinoma. Because surgical resection is not usually done for focal nodular hyperplasia and because that possibility could not be excluded, biopsies of the hepatic mass were considered helpful in the decision regarding subsequent management. Directed percutaneous needle biopsies using peritoneoscopy confirmed that it was a hepatic adenoma.

Because of the risk of intraperitoneal hemorrhage from an adenoma that remained large despite discontinuing oral contraceptive use, surgical resection was recommended. A right hepatic lobectomy was successfully accomplished and was followed by an uneventful postoperative course. Histologic examination of the resected specimen revealed multiple encapsulated adenomatous nodules (Figure 1, top) and areas of hemorrhage thought to correspond to the sites of the needle biopsies. Microscopic examination of tissue sections from a crescent-shaped zone on the superior margin of the largest nodule (Figure 1, top) showed features of a well-differentiated hepatocellular carcinoma. There was definite invasion of tumor cells beyond thickened peripheral vascular structures, with the resultant location of cells immediately adjacent to a portal tract (Figure 1, bottom). The liver not involved with tumor was normal.

Discussion

Epidemiologic data have shown a clear association between hepatic adenoma and oral contraceptive use.[4] It is estimated that more than 50 million women in the United States have been or are currently taking oral contraceptives.[5] Despite this widespread use, the incidence of hepatic adenoma is low.[6] Large hepatic adenomas are frequently symptomatic, and about a third initially present with intraperitoneal hemorrhage.[6] Therefore, surgical resection has been advocated to prevent this complication. Small adenomas are usually found incidentally at an operation or during hepatic imaging. Adenomas may regress with the discontinuation of oral contraceptive use.[7]

Although cases of adenoma with coexistent or transformed hepatocellular carcinoma were reported previously, to our knowledge this is the first case reported in an asymptomatic woman who had been taking contraceptives long term. Our case differs from that reported by Gordon and co-workers in which hepatocellular carcinoma developed at the site of contraceptive-induced hepatic adenoma that had regressed when contraceptive use was discontinued.[8] In the case reported by Gyorffy and associates, the outcome was not known.[3] Despite these differences, we think that our case provides further evidence supporting the concept of the transformation of hepatic adenoma to hepatocellular carcinoma. The histologic features of invasion in the resected specimen

in our patient clearly distinguish hepatocellular carcinoma from hepatic adenoma with dysplasia.[9]

Our case also demonstrates the dilemma in making decisions regarding management in this asymptomatic woman. The difficult decision to proceed with hepatic resection was based on the demonstration of adenoma at biopsy, the large size of the lesion despite the discontinuation of oral contraceptive use, and the increased selective uptake of gallium by the tumor, a finding suspicious for malignancy. The early diagnosis and the right hepatic lobectomy maximized the probability of a cure in this young woman.

The role of progestins in the development of hepatocellular carcinoma in our patient is uncertain. Hepatocellular carcinoma has been reported in patients treated with anabolic steroids,[10] and androgens have a chemical structural similarity to progestins.[11] We can only speculate that in our patient, the ingestion of progestins for six years after discontinuing the estrogen-containing medications may have contributed to the transformation to hepatocellular carcinoma.

It is fortuitous that ultrasonography in our patient included the liver and thus identified the lesion. Of great concern is the observation that hepatocellular carcinoma can occur without symptoms, elevated serum α-fetoprotein levels, or radiologic evidence for malignancy. What is not clear is whether women using oral contraceptives long term need to undergo surveillance ultrasonography. The potential cost-benefits of carrying out such surveillance will be diminished by the identification of many common incidental tumors, such as cavernous hemangiomas, that will necessitate additional scanning tests. Besides, the anxiety associated with the identification of these hepatic lesions may lead to unwanted interventions, including surgical intervention, with their attendant complications. Because the risk of hepatic adenoma developing in women taking oral contraceptives increases with prolonged use,[12] a pilot study targeting the population at risk may provide guidelines to clarify this issue.

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Radiologic Case

Acute Mediastinal Widening Following Endotracheal Intubation and Gastric Lavage

KRISHNAN PADMANABHAN, MD; HARI GADDE, MD; *and* SAMIR VORA, MD, *Brooklyn, New York*

A "Radiologic Case" is published in this format on a regular basis. Physicians interested in contributing to the series are encouraged to send their radiologic cases to the series' assistant editor.

JONATHAN M. LEVY, MD
Assistant Editor

A 57-year-old woman was admitted to hospital with altered sensorium due to a drug overdose. After a difficult endotracheal intubation, gastric lavage was done, and the patient was placed on a respirator. A few hours later, subcutaneous emphysema was noted. A chest x-ray film at that time was normal.

Two days later, the subcutaneous emphysema had resolved and the patient was weaned from the respirator, but high fever and leukocytosis developed. A second chest x-ray film (Figure 1) was obtained, and this led to a computed tomographic (CT) scan of the chest (Figure 2).

Figure 1.—The chest film shows widening of the superior mediastinum. Extension of the process above the clavicle indicates that the mass is located in the posterior aspect of the superior mediastinum.

What are the findings on the chest film?

What diagnosis does the CT scan suggest?

How can the diagnosis be established?

SEE FOLLOWING PAGE FOR DIAGNOSIS AND DISCUSSION

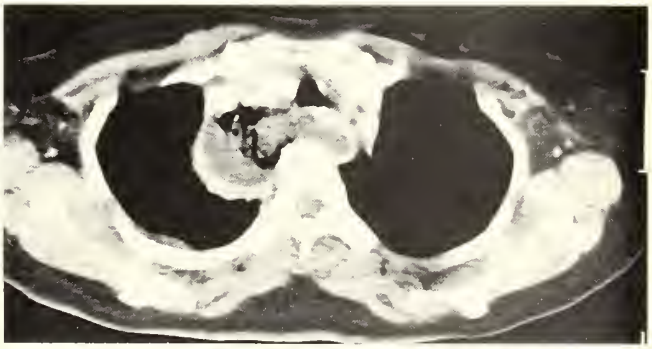

Figure 2.—The computed tomographic scan confirms the posterior location of the mass noted on the chest film and shows fluid and air within the mass, as well as a thick wall. The mass is posterior to the trachea and surrounds the esophagus.

(Padmanabhan K, Gadde H, Vora S: Acute mediastinal widening following endotracheal intubation and gastric lavage. West J Med 1991 Oct; 155:419-420)

From the Pulmonary Department, Coney Island Hospital, Brooklyn, New York (Drs Padmanabhan, Gadde, and Vora), and the Department of Medicine, State University of New York, Health Science Center at Brooklyn, College of Medicine (Dr Padmanabhan).

Reprint requests to Krishnan Padmanabhan, MD, Pulmonary Department, Coney Island Hospital, 2601 Ocean Parkway, Brooklyn, NY 11235.

ANSWER: Esophageal perforation, with mediastinal abscess

The presence of a thick-walled air- and fluid-containing mass adjacent to the esophagus is strong evidence for esophageal perforation with abscess formation. The findings of the CT scan said to be suggestive of perforation include air in the mediastinal soft tissues surrounding the esophagus, mediastinal or pleural abscess cavities adjacent to the esophagus, or communication of the air-filled esophagus with a mediastinal or paramediastinal air-fluid collection. In the presence of any of these findings, a normal esophagogram does not exclude the diagnosis and endoscopy should be done.

Classic findings of cervical esophageal perforation include neck pain, dysphagia, cervical subcutaneous emphysema, and superior mediastinal widening on a chest x-ray film. Esophagoscopy, dilatation of the esophagus, the passage of esophagogastric tubes, and endotracheal intubation all have the potential to cause esophageal injury and perforation. The site of perforation is usually in the posterior midcervical esophagus, in the region of the cricopharyngeus muscle, where the mucosa is supported only by fascia and the lumen is narrow. When the diagnosis is suggested by chest film or CT scan, contrast esophagography or endoscopy, or both, can confirm the diagnosis.

An early recognition of paraesophageal abscess formation is essential so that treatment with cervical mediastinotomy and closure of the perforation can be accomplished. A delay in diagnosis and treatment results in a high incidence of morbidity and mortality as a result of mediastinitis, empyema, and septic shock. Our patient had endoscopy, which showed a 7-mm tear in the posterior midcervical esophagus. She underwent cervical mediastinotomy and closure of the perforation.

Editorials

More Great News for Readers

OUR FUTURE DEPENDS upon our young people. As we teach them, we learn from them; as we guide them, they refresh us. They follow us; they lead us.

In the interest of teaching and learning and leadership, the journal plans to publish periodic sections written by medical students, intended to be read by all. Co-editors Valentina Chen and Robert Cutler, MD, have found deep wells of interest among medical schools and are ready to tap these wells. Ms Chen is a third-year student at the Stanford University School of Medicine. Her undergraduate years were spent at the Johns Hopkins University and Peabody Institute, where she earned a Bachelor of Arts degree in Biophysics and an advanced degree in piano, respectively. She was editor-in-chief of an undergraduate literary magazine. Dr Cutler is Professor of Neurology and Neurological Sciences and Senior Associate Dean for Faculty Affairs at the Stanford University School of Medicine. He attended Harvard College, Tufts University School of Medicine and trained at the University of Chicago where he served on the faculty before moving to Stanford. The following editorial outlines the new section's content and procedures. We welcome your participation as authors, reviewers, and, best of all, readers.

LINDA HAWES CLEVER, MD

Medical Student Section

THE WESTERN JOURNAL OF MEDICINE is pleased to announce the introduction of a new Medical Student Section beginning in 1992. The student section will contain materials written exclusively by medical students. Emphasis will be placed on articles of interest and relevance to practicing physicians. Clinical reviews and results of student research, as well as articles on health care, medical education, and international health are some examples. The section will also contain nonscientific works such as poetry, graphics, photography, editorials, student public service projects, and personal reflections on life in medical school.

The Medical Student Section will appear in the journal on a quarterly basis beginning in January 1992. Manuscripts submitted for publication will be reviewed initially by the editors of the student section, Valentina N. Chen, Stanford University medical student III, and Robert W. P. Cutler, MD, Senior Associate Dean for Faculty Affairs, Stanford University, and then peer-reviewed by experts in the related field.

Submissions currently are being accepted. All manuscripts (and further inquiries) should be sent to Valentina N. Chen, THE WESTERN JOURNAL OF MEDICINE, 221 Main Street, San Francisco, CA 94105. When preparing material for the Medical Student Section, please refer to the Instructions for Authors included in each issue of the journal.

VALENTINA N. CHEN
ROBERT W. P. CUTLER, MD
Stanford University School of Medicine
Stanford, California

A Lethal Leviathan—*Vibrio vulnificus*

ONE OF THE MAJOR HAZARDS resulting from the consumption of such gastronomic delights as raw shellfish is the potential exposure to a myriad of bacterial, viral, or parasitic pathogens or to toxins secreted by dinoflagellates.[1] Although illnesses caused by Norwalk and hepatitis A viruses are by far the most frequent infections associated with raw shellfish ingestion, these virally induced syndromes are usually self-limiting and do not pose serious long-term side effects or result in secondary sequelae as a consequence of their primary infections. In contrast, however, and as highlighted in the review article by Koenig and co-workers in this issue,[2] *Vibrio vulnificus* infections can be devastating and life-threatening if prompt medical recognition and intervention are not forthcoming.

Vibrio vulnificus is a halophilic organism existing in a number of marine habitats (water, sediment, shellfish) from Maine to the state of Washington; it is rarely, if ever, recovered from freshwater samples. Environmental studies of this bacterium indicate that high concentrations are normally associated with warmer coastal waters such as those found in the Gulf of Mexico and along the lower Atlantic seaboard from the Carolinas to Florida. Not well known is the fact that many environmental vibrios, some of which are currently unnamed, are phenotypically similar to *V vulnificus* and cannot invariably be separated using simple biochemical procedures. This fact complicates the analysis of the environmental frequency, distribution, and concentration of this bacterium.

Originally described in a seminal study performed by the Centers for Disease Control in 1976,[3] *V vulnificus* is one of only a handful of the more than 30 known *Vibrio* species that are pathogenic for humans. Fortunately, *V vulnificus* possesses unique phenotypic properties (lactose fermentation *o*-nitrophenyl-β-D-galactopyranoside–positive) that aid in its immediate recognition and separation from other clinically important but less pathogenic members. Retrospective analyses of biochemical data on *Vibrio parahaemolyticus* organisms recovered from cases of fulminant invasive infection before the recognition of this species indicate that many of these septic episodes were not due to *V parahaemolyticus* but rather to *V vulnificus*.

In the original studies by the Centers for Disease Control and as outlined in the current review article, the hallmark of this organism is invasive disease. This attribute has been repeatedly emphasized by the coining of such phrases as "monster from the deep," "Neptune's revenge," and "gastronomic hazard" associated with various reports on the invasive nature of this bacterium.[4] Since its original designation as a species in 1979, *V vulnificus* has emerged as one of the three leading species (along with *Vibrio cholerae* and *V parahaemolyticus*) involved in human disease and, with *V cholerae* non-01, accounts for 95% of all septicemic infections reported to the Centers for Disease Control involving vibrios.[4] In almost all cases of *V vulnificus* septicemia, dissemination has arisen through antecedent attachment and colonization of the gastrointestinal tract after the consumption of raw shellfish, particularly oysters. Persons most prone to the development of such systemic infections include those with hepatic disease (cirrhosis, hepatitis, chronic alcoholism), cancer, or hyperferremia (hemochromatosis, thalassemia). Surprisingly, only a few instances of *V vulnificus* bacteremia have been documented in patients with the acquired immunodeficiency syndrome (AIDS) or AIDS-related complex. An additionally intriguing observation is

the failure of most studies on *V vulnificus* bacteremia to document gastroenteritis in as many as 50% of the patients studied immediately preceding their septic episode. This suggests that either many *V vulnificus* strains produce minimal gastrointestinal symptoms or that they multiply to such a minor extent in the bowel before invasion and dissemination through the mucosa that overt infection does not occur. Regardless, few studies have reported the isolation of *V vulnificus* from feces in patients with bacteremia.

Wound infections caused by *V vulnificus* most often occur in persons who have introduced the bacterium into traumatized external sites during commercial (fishing, crabbing, shucking oysters) or recreational (boating, wading) use of marine facilities. For those without underlying disease, infections are not life-threatening, do not disseminate, and respond to appropriate treatment including antimicrobial therapy and debridement. In rare instances, apparently healthy persons have had fulminant wound infections develop that have led to septicemia and a fatal outcome. For persons with underlying illnesses, the prognosis is much poorer because wound infections in them often rapidly progress to bacteremia with a high mortality rate.

The third syndrome described in the article by Koenig and associates, gastroenteritis, is controversial at best. To date, only two articles have been published that describe a tenuous association between the recovery of *V vulnificus* from stool specimens and gastrointestinal symptoms. In the larger of these two investigations, five of the seven persons with diarrhea and cultures positive for *V vulnificus* simultaneously harbored other recognized or reputed enteropathogens (including *Shigella* species) in their stools.[5] Furthermore, there is anecdotal information in the literature to suggest that *V vulnificus* can be asymptomatically carried in the gut, and there is little in vitro evidence of an enteropathogenic mechanism, although enterotoxin production in rabbit ileal loops has been described.

Probably the most frustrating aspect of this bacterium is the current lack of correlation between its in vitro and in vivo pathogenicity. The in vivo passage of *V vulnificus* in mice enhances pathogenicity, as does the administration of strains to iron-overloaded mice; a direct correlation in patients with hyperferremia or hepatic dysfunction has not been demonstrated, however. In addition to those virulence characteristics described in the article of Koenig and colleagues, *V vulnificus* has been reported to produce other cell-associated or extracellular factors such as pili, hemolysins, a mucinase, chondroitinase, and hyaluronidase; none of these has been directly linked to clinical infections. Unfortunately, the most recent genetic studies on the *V vulnificus* cytolysin, once thought to be a critical factor in virulence, now indicate that it plays a much reduced role in pathogenicity.[6] Probably the most attractive candidate at present is the acidic mucopolysaccharide capsule of *V vulnificus*.[4] Present in virulent strains, spontaneous mutants lacking this factor are nonpathogenic in mice, and acapsular isogenic mutants constructed in vitro through transposon mutagenesis show decreased resistance to the bactericidal activity of normal serum and are less virulent in the mouse model.[7] A direct correlation with in vivo pathogenicity is lacking, however, and most pathogenic strains (encapsulated; opaque colony) undergo phase variation in vitro to a nonpathogenic form (acapsular; translucent colony). What occurs in vivo during the infection process is presently unknown.

Over the past 15 years, our knowledge of the microbiology, environmental distribution, clinical syndromes, and susceptible patient populations associated with *V vulnificus* has significantly increased. On the down side is the fact that little progress has been made in the areas of environment-to-human transmission of this microbe, on the pathophysiology of infection, and on the important variables that regulate the virulence and pathogenic potential of this invasive bacterium. Currently there is a dearth of information on what concentrations of *V vulnificus* in raw seafood are required to elicit clinical disease (infectious dose). Also troublesome is the fact that, like *V parahaemolyticus*, strains of *V vulnificus* recovered from raw shellfish do not match the biotype of patient isolates even when the environmental strain is recovered from the same lot of seafood as that consumed by the affected person. How differences observed in the virulence potential of *V vulnificus* strains in vitro translate to the in vivo situation and transmissibility from environmental sources (infectivity) is also unknown. It is hoped that research in these areas over the next five years will answer some of these questions.

Overall, *V vulnificus* does not pose a serious health risk to the general population, but, for certain highly susceptible persons (liver disease, hyperferremia), efforts should be directed toward the education of these persons to avoid eating raw shellfish, in particular raw oysters, irrespective of current culinary trends. In septic persons with a food, recreational, or travel history documenting possible exposure to the marine environment or its by-products, *V vulnificus* infection should always be considered in the differential diagnosis because of the rapid progression of such infections to lethal results. In addition, one recent alarming note is a report of *V vulnificus* septicemia in persons with no known exposure to seafoods or the ocean.[8] Because of this, it is imperative that Gram's stains of blood cultures displaying curved bacilli with or without pleomorphic forms (coccal, bulbous) be reported as suspicious for the presence of *Vibrio*. Once colonies are identified and in view of the limited number of *Vibrio* species associated with sepsis (*V cholerae* non-01, *V vulnificus*), rapid tests (oxidase, indole, and *o*-nitrophenyl-β-D-galactopyranoside–positivity) can lead to a presumptive diagnosis of *V vulnificus* bacteremia, and appropriate medical staff can then be alerted. With concerted educational, diagnostic, and research efforts geared toward the prevention and treatment of systemic *V vulnificus* infections, the deadly punch of this "sea monster" can be diminished in the near future.

J. MICHAEL JANDA, PhD
Microbial Diseases Laboratory
California Department of Health Services
Berkeley

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Molecular Advances in Retinitis Pigmentosa

IN THIS ISSUE of the journal, Farber, Heckenlively, Sparkes, and Bateman discuss the recent advances in the molecular biology of retinitis pigmentosa.[1] Retinitis pigmentosa and allied disorders are a group of hereditary diseases of the retina and choroid wherein retinal function is retained during the earlier years but eventually is lost as progressive cell dysfunction and cell death occur, resulting in blindness from loss of side vision, central visual acuity, or both.[2] This disorder is a leading cause of untreatable blindness in the young and early adult years. Classic retinitis pigmentosa can be inherited as either an autosomal recessive, autosomal dominant, or X-linked trait. Allied disorders include choroideremia, which is an X-linked recessive disorder, and gyrate atrophy, which is an autosomal recessive disease; both involve total vascular atrophy of the choroid and retina.[3] Retinitis pigmentosa can also be associated with systemic findings as part of a syndrome. Examples of syndromal association include the disorder as part of the Usher syndrome (congenital partial or profound deafness and retinitis pigmentosa), the Bardet-Biedl syndrome (congenital obesity, hexadactyly, hypogenitalism, the presence or absence of mental retardation, and retinitis pigmentosa), Alström's syndrome (diabetes mellitus, obesity, hypogenitalism, and retinitis pigmentosa),[4] and neuronal ceroid lipofuscinosis (also called Batten disease: retinitis pigmentosa, progressive gray matter deterioration, seizures, and early death).

Until recently, of the about 100 diseases grouped as retinitis pigmentosa and allied disorders, only 3 were understood at the biochemical or molecular level. Refsum disease was first described in 1946 under the name heredopathia atactica polyneuritiformis[5] and is associated with a defect in the α-oxidation of phytanic acid, causing the accumulation of this 20-carbon, fully saturated, branched-chain fatty acid in tissues, including the heart, nervous tissue, and the retina; in the retinal tissue, dysfunction and cell death finally cause blindness.[6] Other features include cerebellar ataxia, peripheral neuropathy, nerve deafness, ichthyosiform skin changes, and epiphyseal dysplasia. Cardiac conduction defects leading to arrhythmias are a major cause of early death in Refsum disease. Plasmapheresis may be required to lower plasma levels in acute cardiac toxicity, which can occur when phytanic acid is released from fat stores during fasting. Restricting phytanic acid from the diet can reduce serum phytanic acid levels to normal and has been associated, if acceptable levels can be maintained, with the preservation of vision.[7]

Abetalipoproteinemia is a systemic disease associated with acanthocytosis, progressive neurologic disease, and retinal degeneration.[8] Because of an inability to form chylomicrons, persons with this disorder usually present in infancy or early childhood with steatorrhea and intestinal malabsorption. A good screening test for abetalipoproteinemia is the serum cholesterol level, which, in patients with the disease, is extremely low, often less than 1.13 mmol per liter (50 mg per dl). Because of the absence of chylomicrons, fat-soluble vitamins A, E, and K cannot be transported from the intestinal lymphatics to the liver, and serum levels of these vitamins are extremely low. Treatment with large doses of vitamin A and E can slow or halt the progression of neurologic and retinal disease.

Gyrate atrophy of the choroid and retina is an autosomal recessive dystrophy[3] caused by a deficiency of the mitochondrial matrix enzyme, ornithine δ-aminotransferase (OAT), resulting in a failure of the conversion of ornithine to α-ketoglutarate and a failure of the production of proline.[9] Ornithine levels in serum reach 10 to 20 times normal. This enzyme is a pyridoxal phosphate-dependent enzyme system, and both vitamin B_6-responsive and -nonresponsive forms of gyrate atrophy have been reported. The molecular genetics of the inactivation of OAT have been recently studied.[9]

Rhodopsin is the photoreceptor visual pigment of the rods. Human retinas have about 100 million rods and 20 million cones. The gene for rhodopsin is known to lie on the long arm of chromosome 3.[10] Linkage studies of a large family in Ireland with autosomal dominant retinitis pigmentosa found strong, tight linkage to an anonymous DNA marker called C17,[11] which was known also to reside on chromosome 3. Because C17 and rhodopsin were also linked loosely to a third locus on chromosome 3 at about the identical linkage distance, Dryja and co-workers sequenced the gene directly for rhodopsin in autosomal dominant families with retinitis pigmentosa and found a C-to-A transversion in the second base pair of codon 23 of the rhodopsin gene.[12] This mutation, which, using an allele-specific oligonucleotide, was subsequently found to be present in about 12% of 150 families, changes the sequence to code for a proline residue instead of a histidine. The molecular defect was not found among normal persons or among unaffected members of the families. Indeed, when visual pigments and opsins of other species are screened, the proline at codon 23 is found to be well conserved in nature, again substantiating the defect as the cause of retinitis pigmentosa in these families. Soon thereafter, Dryja and associates described three other molecular defects of the rhodopsin gene in patients with autosomal dominant retinitis pigmentosa.[13] At present, at least 30 separate molecular defects of the rhodopsin gene have been discovered, accounting for about 18% of all families with autosomal dominant retinitis pigmentosa.[14]

The tolerance of the rhodopsin gene to mutation is similar to that seen with the globin gene. Autosomal dominant retinitis pigmentosa does not appear to alter life expectancy or reproductive fitness. At present, how the specific molecular mutations alter rhodopsin physiology and produce cell dysfunction and eventual death is not well understood. The gene product appears, in general, to tolerate missense mutations over most of its amino acid sequence. Missense mutations in the region of the retinal binding site, however, such as Lys296Glu, appear to cause a more severe form of retinitis pigmentosa with no demonstrable rod function even at a young age.[15,16]

Cone dysfunction, cone cell death, and functional, if not virtual, blindness eventually develop in patients with this disease. It is difficult to understand how a defect in rod rhodopsin results in eventual dysfunction and cell death of cones as well. Theories have included the release of toxic products from degenerating rods or even sympathetic degeneration of cones. A transgenic mouse model has been created using the abnormal Pro23His mutation of rhodopsin,[17] and new transgenic mice models are being created for the other rhodopsin mutations. Future studies on these animals offer the hope of discovering the pathophysiology of how the molecular mutations cause retinal dysfunction and cell death. These studies promise new insights into the functions of cell regulation, maintenance, regeneration, and physiology.

Although no animal model exists in the wild that has a direct correlate in humans, the gene defects have recently been described at the molecular level for two mouse models for retinitis pigmentosa. Farber and colleagues at Jules Stein Eye Institute (Los Angeles, California) have for years studied the mouse model *rd*. This disorder begins with elevated cyclic nucleotide levels within the retina, followed later by progressive cell dysfunction and death.[18] The biochemical defect was uncovered by Farber's laboratory to be the enzyme phosphodiesterase, which is crucial for the regulation of the cyclic nucleotide cascade that is initiated by the process of visual excitation of the rod photoreceptor disc membranes.[19] Recently this same group found the β-subunit of phosphodiesterase to be the molecular defect in the *rd* mouse.[20] Although not confirmed as a primary defect, elevated levels of cyclic nucleotides were noted by the UCLA group in the retina of an eye from a person with autosomal dominant retinitis pigmentosa.[21] Travis and co-workers recently discovered that the gene responsible for the mouse model *rds* was the protein specific for photoreceptor outer segments called peripherin.[22] Peripherin is the gene product that helps photoreceptor outer segments form their membranes into discs. Retinas from *rds* mice show distorted, ballooned membranes instead of the normal discs.

Still, if those forms of retinitis pigmentosa that are known to result from mutation of the rhodopsin gene are excluded, this leaves 82% of cases of autosomal dominant, all forms of autosomal, and X-linked retinitis pigmentosa as undefined at the molecular level. At least two and possibly three genes for the disease reside on the short arm of the X chromosome, one at Xp11 and the other at Xp21.[23] Several candidate genes for retinitis pigmentosa are currently being investigated. Most, if not all, of these candidates are genes that are involved in either phototransduction, rhodopsin renewal, or rhodopsin regeneration. Specific candidate genes include the different subunits of G proteins (rod and cone transducins), the S antigen, the subunits of rod and cone cyclic guanosine monophosphate-phosphodiesterases, and several intracellular and extracellular retinoid binding proteins. Studies are now under way to screen families with autosomal recessive retinitis pigmentosa for defects of these candidate genes.

RICHARD G. WELEBER, MD
Professor of Ophthalmology and Medical Genetics
WILLIAM H. MURPHEY, PhD
Coordinator of Oregon Retinitis Pigmentosa Center
Oregon Health Sciences University
Portland, Oregon

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Niacin—The Long and the Short of It

NIACIN IS ONE of the most effective agents for reducing levels of low-density lipoproteins and the triglyceride-rich lipoproteins of plasma. Experience with niacin for this indication now extends beyond 40 years. It is the only drug so far associated with increased survival in an intervention trial.[1] It has been shown to be synergistic with lovastatin and the bile acid-binding resins, leading to the development of combined regimens of unprecedented effectiveness.[2] The synergism of niacin with both of the other agents is such that therapeutic effectiveness can often be achieved at a fraction of the dose required if niacin is used alone. It appears to be the most effective agent available for lowering plasma levels of the Lp(a) lipoprotein. Furthermore, two recent quantitative angiographic trials using combined drug regimens that included niacin showed considerable regression of atherosclerotic lesions in the coronary arteries.[3,4] In evaluating the cost effectiveness of strategies of intervention in atherosclerosis, the extremely low cost of niacin makes it an attractive agent.

Niacin use, however, has a number of side effects with which physicians should be well acquainted if patients are to be successfully maintained on the drug therapy. Virtually all patients experience cutaneous flushing. This prostaglandin-mediated phenomenon can be mitigated substantially by slow, stepwise increases in dosage, beginning with 100 mg two or three times a day, by the administration of 150 to 300 mg of aspirin half an hour beforehand, and by taking the drug

with food. Similarly, a single dose of ibuprofen in the morning will blunt the reaction for much of the day. In most patients, tachyphylaxis to the flushing develops within a few days or weeks, such that they only occasionally experience it after the target dosage regimen is achieved. Some patients have gastric irritation, usually relieved by taking the drug with food and by the use of calcium carbonate as required. Antacids containing aluminum hydroxide should be avoided because the aluminum ion delays the absorption of the nicotinate ion. About 20% have hyperuricemia, which does not require treatment unless gout or urolithiasis supervenes. In clinical experience, allopurinol appears compatible with niacin when needed. A few patients, chiefly those with latent maturity-onset diabetes mellitus, have hyperglycemia while taking niacin. Whereas most revert to normal when the medication is discontinued, the failure of a few to do so urges close monitoring of blood glucose levels. Perhaps a fourth of persons receiving crystalline niacin will have mild elevations of aminotransferase activity and occasionally alkaline phosphatase activity during treatment. There is reason to think that some asymptomatic elevations in aminotransferase activity up to three times the upper limit of normal may be a reflection of enzyme induction and not due to parenchymatous liver damage. It is our practice to measure the aminotransferase activity in these patients at frequent intervals without discontinuing the drug. A few patients present with a much more severe clinical syndrome that indeed suggests chemical hepatitis. These patients have anorexia, often nausea and vomiting, and may have inordinately low serum lipid values, perhaps due to a pronounced reduction in hepatic lipoprotein secretion. They have mild to marked elevations of aminotransferase activity in plasma and occasionally show clinical and chemical evidence of cholestasis. Niacin therapy should be discontinued in such patients.

Reversible chemical hepatitis has long been recognized in some patients receiving crystalline niacin, usually at doses of more than 3 grams per day.[5,6] Electron-microscopic studies have shown moderate dilation and deformity of the tubular structure of the rough endoplasmic reticulum even in patients without abnormality in tests of liver function. Similar changes have been described with other widely used pharmaceutical agents. There is no evidence, however, that such changes progress to advanced hepatic parenchymal disease in patients who do not have evident chemical hepatitis. In our experience, liver function test results do not tend to change in more than a decade of continuous treatment with crystalline niacin. In contrast, a number of reports have appeared describing serious or even fulminant hepatitis associated with the use of sustained-release niacin preparations.[7-12] The report by Fischer and co-workers in this issue of the journal adds an account of such a case leading to a fatal outcome.[13] In one case, the patient's life was saved only by a timely liver transplant.[7] In another, the inciting dose was only 500 mg per day.[8] In several cases, severe hepatitis developed in less than a week.[7,10] Where patients were readministered crystalline niacin, hepatic dysfunction did not recur.[10,11]

Several sustained-release preparations of niacin have been developed to minimize the cutaneous flushing associated with the drug. Such preparations are now being promoted by several large drug chains, almost to the exclusion of regular or crystalline niacin. We add here a brief account of an additional case referred to the University of California, San Francisco, Lipid Clinic because of severe hepatotoxicity. The patient, a 52-year-old physician with a history of Gilbert syndrome, normal aminotransferase activity, and combined elevations of plasma cholesterol and triglyceride levels, was treated for more than a year with 500 mg of timed-release niacin (Walgreen) twice a day without symptoms. He had no exposure to any known hepatotoxins. In August 1990, he awoke with moderately severe epigastric pain that lasted for several hours during which he took one tablet each of cimetidine and ranitidine. The following day, his liver function test results were as follows: aspartate aminotransferase 6,370 U per liter (normal 3 to 45), alanine aminotransferase 2,440 U per liter (normal 3 to 48), lactate dehydrogenase 2,860 U per liter (normal 60 to 200), γ-glutamyl transferase 237 U per liter (normal 2 to 56), alkaline phosphatase 140 U per liter (normal 2 to 56), direct bilirubin, 24 μmol per liter (1.4 mg per dl), indirect 34 μmol per liter (2.0 mg per dl). Glucose, creatinine, and electrolyte levels and hemogram values were normal. The total serum cholesterol and triglyceride levels were 4.3 and 0.66 mmol per liter (166 and 59 mg per dl), respectively. Antibodies to hepatitis A and B were undetectable. The niacin therapy was discontinued. Five days later, the aspartate and alanine aminotransferase, lactate dehydrogenase, and alkaline phosphatase activities were 94, 360, 160, and 93 U per liter, respectively, and they were all normal within three weeks. The patient has declined a rechallenge with crystalline niacin.

Whether the fulminant hepatitis associated with the use of sustained-release niacin results from the same mechanism as the milder form of hepatic dysfunction encountered with the crystalline form of the drug is indeterminate at this time. Because chemical hepatitis has been associated with preparations that retard release by complexing the niacin with resin or with aluminum ion, or even by highly compressing the tablets, it would appear that the time course of the exposure of liver to niacin is the critical factor.[14] Therefore, no sustained-release strategy can be expected to be safe in this respect. A possible cause for this phenomenon may lie in the complex metabolites of niacin that are formed by the liver. These include niacinamide, nicotinuric acid, two isomeric carboxamides, and methylated derivatives. The ratios of these metabolites are known to differ significantly with the dose of niacin. Thus, prolonged exposure of the liver to the drug may favor the accumulation of a toxic metabolite. An intermittent dosage may allow the restoration of some critical function of the hepatocyte, which is depressed by niacin per se. It is of interest in this regard that niacinamide, too, can induce hepatitis.[15] A further possibility is that a toxic side product may be formed during the manufacture of niacin. It is likely that other factors may potentiate the hepatotoxicity of niacin. In some cases, the development of viral hepatitis could compound the insult to the liver. Perhaps viruses not usually associated with hepatitis could be involved, akin to the situation in Reye's syndrome. The concomitant administration of other drugs might well influence the metabolism of niacin. Based on limited preliminary data, it appears that a modest increase in the risk of hepatotoxicity and of myopathy may occur when lovastatin and niacin are administered together. The striking effectiveness of this combination in treating severe hyperlipidemia warrants its continued use, but physicians should observe these patients closely. Reports of new cases of niacin-associated hepatic dysfunction should include a detailed description of other drugs being taken, including nonprescription drugs. For example, in three cases

described to date, including the one in this report, cimetidine or ranitidine was taken with niacin. A careful history should also be obtained of the consumption of wild mushrooms and exposure to hepatotoxins such as halocarbons.

In our opinion, the severity of chemical hepatitis associated sporadically with sustained-release niacin offsets the limited advantage of diminished flushing in the balance of risk and benefit. Physicians should avoid prescribing sustained-release preparations, counseling their patients instead in other strategies to induce tachyphylaxis to flushing as described earlier. Furthermore, niacin in doses above 100 mg should be regarded as a drug. Ideally, it should be on a prescription status and should be subject to the same scrutiny by regulatory agencies as other prescription drugs. Patients taking niacin should be under the surveillance of a physician who can monitor liver function and other indices of toxicity appropriately. It is also prudent to administer niacin no more than three times a day.

Many of our most effective drugs carry a potential for serious or even life-threatening side effects. Niacin, frequently viewed by the public as a benign food supplement, shares this property. The high therapeutic value of niacin in the treatment of hyperlipidemia and in the prevention of atherosclerosis merits its retention in the pharmacopeia. Our emerging awareness of fulminant hepatitis as a risk of treatment with sustained-release preparations should lead to their discontinuance. Furthermore, all patients receiving niacin should be observed with the same diligence as though they were being treated with a digitalis glycoside or an anticoagulant. Any major adverse effects should be reported to the US Food and Drug Administration.

MARY J. MALLOY, MD
Clinical Professor of Pediatrics and Family and Community Medicine
Cardiovascular Research Institute
Department of Pediatrics

PHILIP H. FROST, MD
Associate Clinical Professor of Medicine
Cardiovascular Research Institute
Department of Medicine

JOHN P. KANE, MD, PhD
Professor of Medicine and Biochemistry
Cardiovascular Research Institute
Department of Medicine
University of California, San Francisco, School of Medicine

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Preceptorships in the 21st Century
The Return of the Apprentice

A PRECEPTORSHIP is an educational experience in which medical students or residents spend a period of time with a physician in a practice setting outside the medical school or teaching hospital. It is meant to be a one-on-one learning assignment that allows students and residents to experience the scope and flavor of the practice of medicine in a physician's office and in the community. It is difficult to know when preceptorships were first officially recognized in the United States medical school curriculum, but we do know that the University of Wisconsin Medical School began a medical student preceptorship in 1926 "as a bold new experience in medical education for senior students." The concept of novices learning at the side of masters is an old one, however, certainly as old as the practice of medicine itself.

In fact, in the pre-Flexner days and before the development of the modern teaching hospital, most medical training in the United States occurred at the side of private practitioners. Because we think that teaching by private practitioners will increase, we have called this predicted trend the "return of the apprentice." This trend is due, in part, to a recognition that ambulatory care should become a more important part of medical training. Many teaching hospitals are already increasing the time spent by medical students and residents in their outpatient clinics.

This shift from inpatient to outpatient teaching is spilling out of the teaching hospital and into private practice to provide students and residents exposure to a greater variety of diseases and disorders. According to a 1979 survey of family medicine departments, 94 of 101 responding medical schools reported offering some type of preceptorship. In 1986, Meadows and co-workers found that 88% of those responding from family medicine, 66% from pediatrics, and 26% from internal medicine departments offered medical school experience in private practices.[1]

The desirability of teaching clinical medicine in the private office was highlighted by a medical school teacher who commented, "Learning primary care in a university hospital is like trying to learn forestry in a lumberyard."[2] This dichotomy between what is taught and what is practiced was described in the well-publicized critique of medical education, the American Association of Medical Colleges' General Professional Education of the Physician Report, "Physicians for the Twenty-first Century," which noted, "Although fewer than five percent of all physician/patient contacts result in hospitalization, clinical clerkships are predominantly based on hospital inpatient services."[3] Thus, we view the "return of the apprentice" as a necessary and desirable trend in medical education with benefits to the physicians-in-training (medical students and residents) and their physician-teachers (preceptors).

The preceptorship provides the physicians-in-training the opportunity to develop insights into the physicians' way of life in a community setting, urban or rural. In a preceptorship, learners come to understand the individual nature of

medical practice and the need for knowing each patient in relation to his or her family and community setting. Students and residents are given the opportunity to attend meetings of local civic organizations and to participate in meetings of county medical societies and community hospital staffs.

As preceptors become a major access point for facilitating future physicians' understanding of and participation in direct patient care and community and professional involvement, they become role models in whom physicians-in-training see the blending of the practice of medicine with personal life-style. In return, there are rewards for both teachers and learners. As one Utah preceptor told us,

> When I think back to my own training experience, I realize that the teachers who impressed me most were those who imparted their style to me. Some of my greatest pleasures come when, at the end of the preceptorship, students say they have learned something special about caring for patients . . . that something of my style has been observed, appreciated, and accepted.[4]

Also, in the give and take with students or residents, perceptors may gain new insights and perspectives, and the preceptorships may provide opportunities for private physicians to keep in touch with medical schools and to widen their scope of knowledge. One Colorado preceptor acknowledged, "Having students and residents around requires that we keep abreast of the latest developments in medicine and be familiar enough with the current literature to cite references when discussing our decisions and strategies."[5]

Although the preceptorship may be a "return of the apprentice," it need not be viewed as a step back into the 19th century. The preceptorship for the 21st century can be well structured with defined goals and objectives. What is learned should not be left to random happenstance. Instead, learning experiences can be designed to take maximum advantage of community-based office practice settings and the types of patient care problems that are seen there.

With the increasing recognition of the value of the preceptorship, more preceptors will be needed. We encourage private physicians to be responsive to requests from medical schools and residency programs for new preceptorship sites. In addition, private practitioners can take an active, rather than reactive, stance by contacting the medical schools in their state or the medical school from which they graduated and volunteering to become preceptors. If medical education is to adequately train physicians for the 21st century, the educational role of private practitioners needs to be increased and expanded.

F. MARIAN BISHOP, PhD, MSPH
Chair

NEAL A. WHITMAN, MPA, EdD
Professor

Department of Family and Preventive Medicine
University of Utah School of Medicine
Salt Lake City, Utah

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Correspondence

The Editors will be pleased to receive and consider for publication correspondence containing information of interest to physicians or commenting on issues of the day. Letters ordinarily should not exceed 600 words and must be typewritten, double-spaced, and submitted in duplicate (the original typescript and one copy). Authors will be given the opportunity to review the editing of their correspondence before publication.

Public Interest in Human Growth Hormone Therapy

To the Editor: Before the availability of synthetic human growth hormone (hGH), the limited supply of pituitary hGH dictated its use. Now that this issue and the risk of infectious contamination have been resolved, hGH is being used in conditions other than classic growth hormone deficiency, such as Turner's syndrome. The decision to treat is no longer based only on hormonal levels but involves such factors as growth velocity, predicted ultimate height, and the concerns of the patient and parents. The largest potential use of growth hormone probably is for short, otherwise normal children who do not have classic growth hormone deficiency.[1] An extension of this process would be to consider the use of human growth hormone to augment the height of children of "normal" stature, an issue of obvious ethical importance.[2]

To determine the nature and effect of public interest in hGH, questionnaires were mailed to 1,291 (17%) of the 7,494 licensed family physicians, general practitioners, and pediatricians in Texas. Six rural and six urban counties were arbitrarily selected as target areas. Of the 517 respondents (40% return rate), 226 (44%) reported an estimated 1,042 inquiries over a five-year period. Parents made 833 (80%) of the inquiries; 92% of these were considered appropriate (short stature) and only 8% inappropriate ("normal" height, athletic enhancement). Although only 209 (20%) of the inquiries were initiated by the patients themselves, nearly half of these (42%) were considered by the physician to be for inappropriate reasons. Only 8 inquiries were for females and 5 for nonwhites.

The data derived from this study should be viewed with caution since the information obtained depended by necessity entirely upon physician recall as well as his or her own interpretation of an "appropriate" inquiry. We think, however, that the scope of the survey was of sufficient magnitude to provide a reasonable estimate of the frequency with which primary care physicians (excluding internists) are approached with questions about human growth hormone.

The results indicate that young white males and their parents are the largest group interested in hGH and the most common reason for inquiry is for short stature. There is a relatively small but definite interest in hGH for athletic enhancement by both parents and patients. Although 44% of respondents reported having at least one inquiry about hGH, the fact that, overall, only 156 (15%) of the 1,042 inquiries were considered "inappropriate" suggests that public interest in hGH (in the region surveyed) is largely for legitimate reasons.

While there is still potential for the misuse of hGH, which could escalate in the future, current interest in the inappropriate administration of this hormone appears to be less than that for anabolic steroids.[3] This may be related to the relatively high cost of hGH, the necessity for parenteral injection, and limited public awareness of the greater availability of the synthetic preparation.

PAUL S. SALVA, MD, PhD
Department of Pediatrics
Indiana University Medical Center
Indianapolis, IN 46223

GEORGE E. BACON, MD
Department of Medical Education & Research
Butterworth Hospital
Grand Rapids, MI 49503

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Tort Reform Works

To the Editor: I read with great interest the article about tort reform in the WAMI states (Washington, Alaska, Montana, and Idaho) by Rosenblatt and colleagues in the June issue[1] and their discussion of the relationship of such reform to access to obstetric care. Although the authors correctly state that it is too early to judge the effectiveness of these reforms, I am concerned that the article might plant in the minds of readers some doubt as to the effectiveness of tort reform in general.

In California our experience under the Medical Injury Compensation Reform Act (MICRA), enacted in 1975, has been so favorable that MICRA is now being used as a model for proposed national legislation and is the centerpiece of changes recently advocated by the President.

Our ability to draw firm conclusions in California rests on two major premises. First, the cap on noneconomic damages and periodic payment of future damages are superior to those in the WAMI states. Our $250,000 cap on noneconomic damages contrasts with Washington, where there is no cap. (A variable cap enacted in 1986 was struck down by the Washington Supreme Court in 1989.) In Alaska the cap is $500,000 with exceptions for physical impairment and disfigurement; in Montana there is no cap; in Idaho the cap is $400,000.

California's provision for periodic payments of both economic and noneconomic future damages applies at the request of either party at a threshold of $50,000. In Washington noneconomic damages must be paid up front. This is an especially adverse feature in view of the striking down of the cap in 1989. In Alaska there is no threshold, but the court is allowed to require periodic payments. In Montana there is no provision for periodic payments; in Idaho the threshold is $400,000.

Among the WAMI states, Montana is worthy of special mention. With the exception of pretrial screening, no major tort reforms exist. Moreover, the effects of the screening panels are further weakened because their findings are not admissible at subsequent trial. We insure most of Montana's doctors and find its tort climate and legal culture to be highly

adverse to medical defendants. Montana—without notable tort reform—should not have been included with the other three states by the authors.

We can draw conclusions regarding the effectiveness of the California reforms because they have been in place for over 15 years, whereas in the WAMI states they are much more recent. There are two reasons for the very long lag between the enactment of tort reforms and the manifestations of their effectiveness. First, the reforms must survive the perception that they are unconstitutional. This required four constitutional challenges and ten years in California. Newly enacted reforms apply only prospectively to cases filed *after* their enactment. Thus, cases that find their way to trial over the next four to five years do not reflect their effect. Additional years need to pass before there are enough cases affected by the reforms to allow any conclusions about their effectiveness. Depending on the speed with which cases come to trial in a given state, this interval is never less than five or six years, and in a state with much litigation and crowded court calendars, the delay can be as long as 10 to 12 years.

Even when reforms have been enacted, until their survival is reasonably certain, insurers must continue to reserve funds on a worst-case basis—that some or all of the reforms could be nullified by subsequent legislation or could be struck down by the courts. Insurers simply cannot chance the possibility of being caught short in their reserves. This explains why insurance premiums do not go down immediately following the enactment of tort reform.

While the debate on tort reform revolves around the small minority (5%) of cases that go to trial, the ultimate effect of reforms must be gauged by those cases that are settled short of trial and on which the trial reforms have an "umbrella" effect. Thus the negotiated cases, where the bulk of the transactions take place, suffer from the same "tort reform lag."

In California, medical malpractice premiums in 1975 were among the highest in the nation. They now stand at 35th, well below the national average. In our company, the average premium (all specialties) has declined 31% in constant 1976 dollars, not counting large policyholder dividends that have been returned which further lower the effective premium. The premium and policyholder dividend history of the other three doctor-owned companies in California is similar. In addition, all four California companies have completely repaid many millions of dollars of the original surplus contributions made by their early members to capitalize the companies. The American College of Obstetrics and Gynecology has stated that premiums for obstetricians and gynecologists in District IX, California, are the lowest in the nation, a point that pertains directly to Rosenblatt and colleagues' article.

Yes, tort reform does work. Our task now in California is to prevent the legislature from overturning all or parts of MICRA. This continues to be a major threat to stable cost and availability of insurance for doctors and, more important, for the protection of their patients.

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REFERENCE

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Medical Tourists

To the Editor: I was intrigued by the conclusions of Fred Wurlitzer's commentary, "Volunteering in West Africa." I admire the spirit that draws Dr Wurlitzer and thousands like him to volunteer their services to those in dire need. Dr Wurlitzer concludes that the interventions of visiting physicians will fail to make a difference to the overall medical conditions in Third World countries unless these visiting physicians address public health measures such as vaccinations and sanitation and the improvement of the indigenous health system.

Despite his conclusion, Dr Wurlitzer seems to encourage physicians to volunteer in the Third World even if they are not in a position to contribute to the aforementioned endeavors. He even underscores the importance of surgical training. I would agree with Dr Wurlitzer that while the rule of rescue calls on physicians to do something to ameliorate the horrible suffering and dying that goes on daily in the Third World, in the long run the visiting clinician probably takes more from the visit in terms of adventure and experience than does the needy community.

What Dr Wurlitzer fails to mention is the potential for the visiting clinician actually to do harm by further highlighting the glamour of Western physicians, detracting from the community's willingness to interact with their own village health worker. This undermines the ability of these "barefoot doctors" to deliver their essential services long after the Western physicians have departed.

The appropriate conclusion from Dr Wurlitzer's experience is that physicians who are intent on truly being of service abroad will focus their efforts on the public health measures so aptly described in the article. Ideally those who volunteer abroad would be able to make a long-term commitment to strengthening and improving the health services in the community they choose to serve. Younger physicians may even wish to acquire training in public health before serving abroad. Perhaps if the full wisdom of Dr Wurlitzer's observations were implemented, then the current press of Third World interlopers would amount to something more than medical tourism.

DAVID BISHAI, MD, MPH
Resident Physician
UCLA Preventive Medicine Dept.
1558 Brockton Ave. #8
Los Angeles, CA 90025

REFERENCE

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* * *

Dr Wurlitzer Responds

To the Editor: Commitments by medical personnel to work in public health for one or more years in Africa are needed. Concerns about the role of the village health worker are valid, but allow me some observations.

Most African national medical professionals are not "barefoot doctors." At the hospitals I attended in Sierra Leone and Zaire, the permanent expatriate staff taught public health, nursing, and surgery. One national, who had no MD degree, did several hundred hernia repairs yearly very well after such practical training. Even if expatriate staffs were to depart, I am confident many nationals would continue medical care and that many communities would continue to react positively to them. In fact, many hospitals exist today in Africa that are run well and entirely by nationals following

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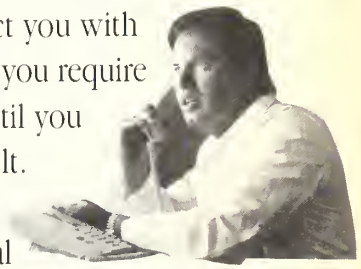

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of precious yellow liquid
which has spilled all over his bottle.

"Great, Dad, keep peeing," I grin
as a male nurse measures
the cloudy liquid.

Bless pee and all men's penises;
old football coaches,
Japanese architects,

young truck drivers, all
with catheters hanging out,
stumbling about, backside showing,

some frontside too,
but mostly bless my father:
Pee for me, Dad, and all fathers

who changed pissy pants
of sons and daughters,
especially daughters; all men

we no longer hear or read about
who never abused us or hurt us,
who gave us their manly gifts

of strength and wisdom,
who loved us
gently with compassion.

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so young so pretty
standing
with her tray of pills
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with Jan and Mag and Dulcie

his mind blurring
the noise of clocks
his brush
almost within reach
the colors perfect
Venetian red
gamboge
that best of all blues
the one called Capri

and his brain throbbing
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Librox 350, 351
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BuSpor 335, 336

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Corduro ..... 2nd cover, 329

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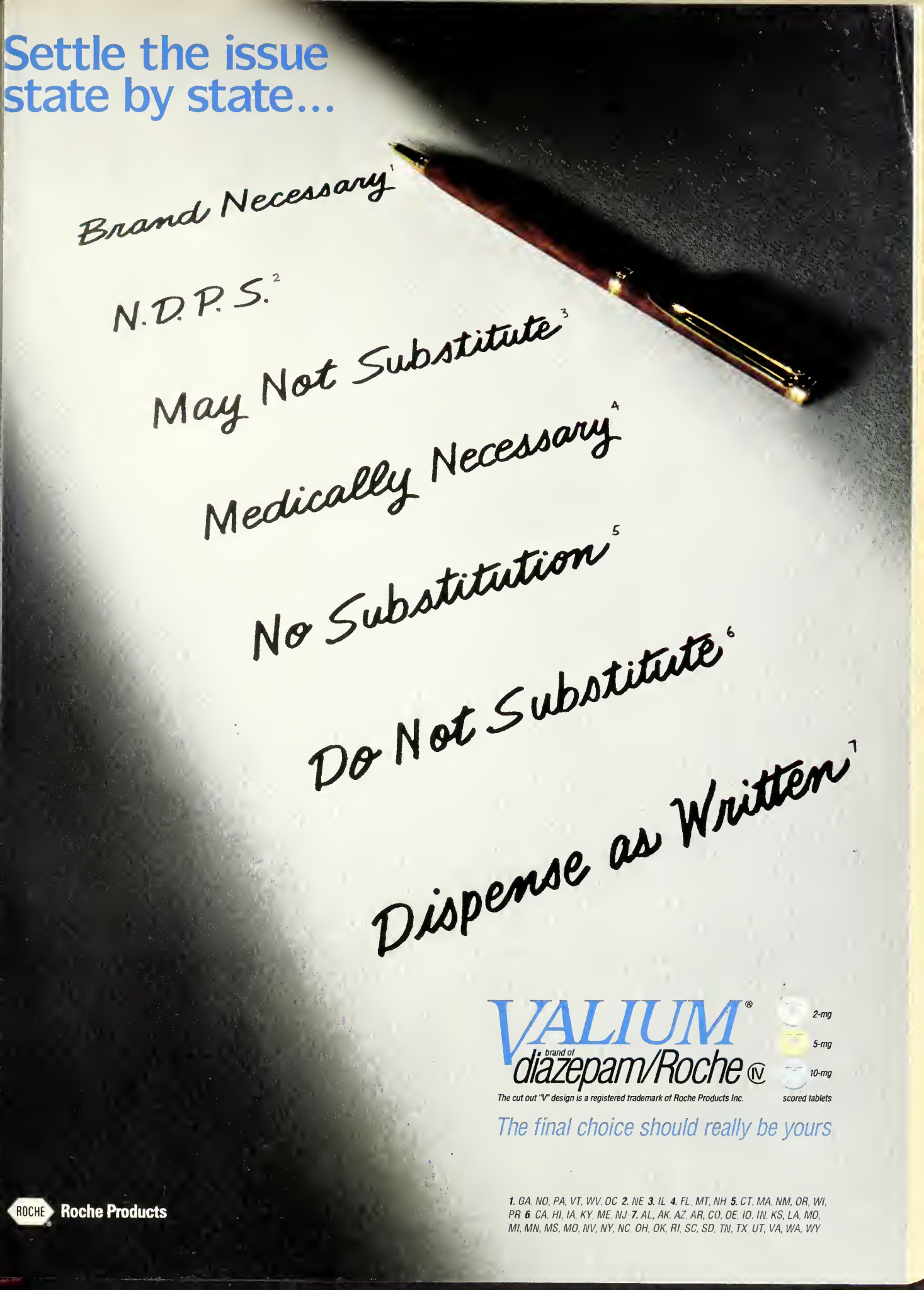
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505 Molecular Mechanisms of Cancer
Moderator: H P KOEFFLER
Discussants: F McCORMICK and C DENNY

EPITOMES

515 Important Advances in Psychiatry

ALERTS, NOTICES, AND CASE REPORTS

525 Aspergillar Myocarditis and Acute Coronary Artery Occlusion in an Immunocompromised Patient
M K HORI, L L KNIGHT, P G CARVALHO, and D L STEVENS

527 Bilateral Spontaneous Renal Hemorrhage Due to Polyarteritis Nodosa
J C PRESTI Jr and P R CARROLL

528 The Numb Chin in Metastatic Cancer
C P HARRIS and J R BARINGER

531 Massive Splenic Infarction in Doubly Abnormal Heterozygous Sickling Disorders—A New Complication of Acute Splenic Sequestration Syndrome
R A BERRY, E A ODUMAKINDE, and J P LEWIS

COMMENTARY

533 Managed-Care Plans—Their Future Under National Health Insurance
T P WEIL

538 Physician, Heal Thy Planet
W B STEWART

EDITORIALS

540 There's a Long, Long Trail A-winding. . . • Physicians and the Human Immunodeficiency Virus • Liver Transplantation—Challenges for the Future • Molecular Genetics in the Cancer Clinic

CORRESPONDENCE

547 Human Immunodeficiency Virus Infection in Children Who Received Transfusions in Mexico • Toxic Exposure to Betamix • Smoking Cessation Attitudes, Practices, and Policies Among California Primary Care Physicians • An Inexpensive, Convenient Adjunct for the Treatment of Diabetes • The Digital Rectal Examination of Women • WARNING—Inhaling Tabasco Products Can Be Hazardous to Your Health

LESSONS FROM THE PRACTICE

551 My Jogging Partner
D F HOCH

553 Heart and Mind
M H CHIN

SPECIAL ARTICLE

555 Memoirs of an Amnesiac—Two Years With Brain Cancer, or the Outer Space of Living With Brain Tumors
A D DOR-NER

OTHER FEATURES

461 In Memoriam

464 Continuing Medical Education Activities in Arizona; California, Hawaii, and Nevada; Colorado; Idaho; New Mexico; Utah; Washington

474 Subscription Information

563 Instructions for Authors

564 Classified Advertising

576 Western State Medical Associations' Meetings

Poems: 504, 537, 539

Detailed Table of Contents: 450, 453, 458

Official Journal of the Alaska State Medical Association, the Arizona Medical Association, the California Medical Association, the Denver Medical Society, the Idaho Medical Association, the Nevada State Medical Association, the New Mexico Medical Society, the Utah Medical Association, the Washington State Medical Association, and the Wyoming Medical Society.

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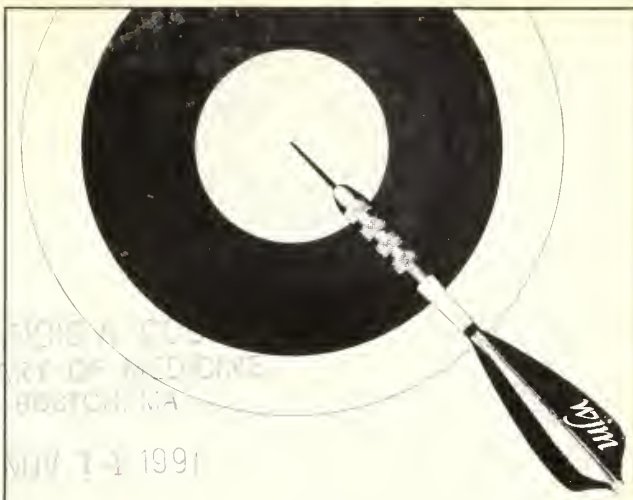

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VOLUME 155 • NUMBER 5 • NOVEMBER 1991

CONTENTS

BIOMEDICAL SCIENCE

481 **The AIDS Virus—What We Know and What We Can Do About It**

FLOSSIE WONG-STAAL, PhD

From the Department of Medicine and Biology, University of California, San Diego, School of Medicine, La Jolla, California.

ARTICLES

488 **Decision Making in Critically Ill Patients With Hematologic Malignancy**

STEPHEN W. CRAWFORD, MD

From the Division of Clinical Research, Fred Hutchinson Cancer Research Center, and the Department of Medicine, University of Washington School of Medicine, Seattle.

494 **Liver Transplantation—Experience With 100 Cases**

JEAN-LUC SZPAKOWSKI, MD; KEN COX, MD; PAUL NAKAZATO, MD; WALDO CONCEPCION, MD; BARRY LEVIN, MD; and CARLOS O. ESQUIVEL, MD, PhD

From the Transplant Institute, California Pacific Medical Center, San Francisco. Dr Szpakowski is now with Kaiser Permanente, Richmond, California.

500 **Recruiting Physicians to Rural Practice—Suggestions for Success**

KATHERINE RILEY, PhD; WAYNE MYERS, MD; and RONALD SCHNEEWEISS, MD

From the Departments of Medical Education and Family Medicine, University of Washington School of Medicine, Seattle, and the University of Kentucky Center for Rural Health, Hazard, Kentucky.

CONFERENCES AND REVIEWS

505 **Molecular Mechanisms of Cancer**

Moderator: H. PHILLIP KOEFFLER, MD

Discussants: FRANK McCORMICK, PhD, and CHRISTOPHER DENNY, MD

An edited summary of an Interdepartmental Conference arranged by the Department of Medicine of the UCLA School of Medicine, Los Angeles. The Director of Conferences is Anthony T. Campagnani, PhD, Professor of Medicine.

EPITOMES—IMPORTANT ADVANCES IN CLINICAL MEDICINE

Psychiatry

Items of progress in psychiatry. Each item, in the judgment of a panel of knowledgeable physicians, has recently became reasonably firmly established, both as to scientific fact and important clinical significance.

515 **Electroconvulsive Therapy**

MAX FINK, MD

516 **Electrophysiologic Evaluation for Brain Dysfunction**

MAURICE RAPPAPORT, MD

516 **Prophylaxis of Antipsychotic Drug-Induced Extrapyramidal Syndromes**

GEORGE A. KEEPERS, MD

517 **Panic Disorder**

DOUGLAS KAHN, MD

518 **Rational Polydrug Use in Psychiatry**

ROBERT GERNER, MD

519 **Tobacco Dependence and Smoke-free Psychiatric Units**

JOHN A. MENNINGER, MD

519 **Eating Disorders in Psychiatric Illness**

BARTON J. BLINDER, MD, PhD

(Continued on Page 453)

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Warnings: Verapamil should be avoided in patients with severe LV dysfunction (eg, ejection fraction < 30%) or moderate to severe symptoms of cardiac failure and in patients with any degree of ventricular dysfunction if they are receiving a beta-blocker. Control milder heart failure with optimum digitalization and/or diuretics before Calan SR is used. Verapamil may occasionally produce hypotension. Elevations of liver enzymes have been reported. Several cases have been demonstrated to be produced by verapamil. Periodic monitoring of liver function in patients on verapamil is prudent. Some patients with paroxysmal and/or chronic atrial flutter/fibrillation and an accessory AV pathway (eg, WPW or LGL syndromes) have developed an increased antegrade conduction across the accessory pathway bypassing the AV node, producing a very rapid ventricular response or ventricular fibrillation after receiving I.V. verapamil (or digitalis). Because of this risk, oral verapamil is contraindicated in such patients. AV block may occur (2nd- and 3rd-degree, 0.8%). Development of marked 1st-degree block or progression to 2nd- or 3rd-degree block requires reduction in dosage or, rarely, discontinuation and institution of appropriate therapy. Sinus bradycardia, 2nd-degree AV block, sinus arrest, pulmonary edema and/or severe hypotension were seen in some critically ill patients with hypertrophic cardiomyopathy who were treated with verapamil.

Precautions: Verapamil should be given cautiously to patients with impaired hepatic function (in severe dysfunction use about 30% of the normal dose) or impaired renal function, and patients should be monitored for abnormal prolongation of the PR interval or other signs of overdosage. Verapamil may decrease neuromuscular transmission in patients with Duchenne's muscular dystrophy and may prolong recovery from the neuromuscular blocking agent vecuronium. It may be necessary to decrease verapamil dosage in patients with attenuated neuromuscular transmission. Combined therapy with beta-adrenergic blockers and verapamil may result in additive negative effects on heart rate, atrioventricular conduction and/or cardiac contractility; there have been reports of excessive bradycardia and AV block, including complete heart block. The risks of such combined therapy may outweigh the benefits. The combination should be used only with caution and close monitoring. Decreased metoprolol and propranolol clearance may occur when either drug is administered concomitantly with verapamil. A variable effect has been seen with combined use of atenolol. Chronic verapamil treatment can increase serum digoxin levels by 50% to 75% during the first week of therapy, which can result in digitalis toxicity. In patients with hepatic cirrhosis, verapamil may reduce total body clearance and extrarenal clearance of digitoxin. The digoxin dose should be reduced when verapamil is given, and the patient carefully monitored. Verapamil will usually have an additive effect in patients receiving blood-pressure-lowering agents. Disopyramide should not be given within 48 hours before or 24 hours after verapamil administration. Concomitant use of flecainide and verapamil may have additive effects on myocardial contractility, AV conduction, and repolarization. Combined verapamil and quinidine therapy in patients with hypertrophic cardiomyopathy should be avoided, since significant hypotension may result. Concomitant use of lithium and verapamil may result in a lowering of serum lithium levels or increased sensitivity to lithium. Patients receiving both drugs must be monitored carefully. Verapamil may increase carbamazepine concentrations during combined use. Rifampin may reduce verapamil bioavailability. Phenobarbital may increase verapamil clearance. Verapamil may increase serum levels of cyclosporin. Verapamil may inhibit the clearance and increase the plasma levels of theophylline. Concomitant use of inhalation anesthetics and calcium antagonists needs careful titration to avoid excessive cardiovascular depression. Verapamil may potentiate the activity of neuromuscular blocking agents (curare-like and depolarizing); dosage reduction may be required. Adequate animal carcinogenicity studies have not been performed. One study in rats did not suggest a tumorigenic potential, and verapamil was not mutagenic in the Ames test. Pregnancy Category C. There are no adequate and well-controlled studies in pregnant women. This drug should be used during pregnancy, labor, and delivery only if clearly needed. Verapamil is excreted in breast milk; therefore, nursing should be discontinued during verapamil use.

Adverse Reactions: Constipation (7.3%), dizziness (3.3%), nausea (2.7%), hypotension (2.5%), headache (2.2%), edema (1.9%), CHF, pulmonary edema (1.8%), fatigue (1.7%), dyspnea (1.4%), bradycardia: HR < 50/min (1.4%), AV block: total 1°,2°,3° (1.2%), 2° and 3° (0.8%), rash (1.2%), flushing (0.6%), elevated liver enzymes, reversible non-obstructive paralytic ileus. The following reactions, reported in 1.0% or less of patients, occurred under conditions where a causal relationship is uncertain: angina pectoris, atrioventricular dissociation, chest pain, claudication, myocardial infarction, palpitations, purpura (vasculitis), syncope, diarrhea, dry mouth, gastrointestinal distress, gingival hyperplasia, ecchymosis or bruising, cerebrovascular accident, confusion, equilibrium disorders, insomnia, muscle cramps, paresthesia, psychotic symptoms, shakiness, somnolence, arthralgia and rash, exanthema, hair loss, hyperkeratosis, macules, sweating, urticaria, Stevens-Johnson syndrome, erythema multiforme, blurred vision, gynecomastia, galactorrhea/hyperprolactinemia, increased urination, spotty menstruation, impotence.

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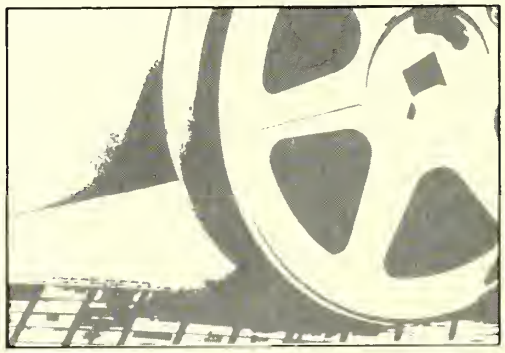

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(Continued from Page 450)

520 **Nocturnal Enuresis**
EBERHARD M. MANN, MD

521 **Treatment-Resistant Depression**
MICHAEL J. GITLIN, MD

521 **Antidepressant Treatment in Patients With Heart Disease**
RICHARD D. LANE, MD

522 **Obsessive-Compulsive Disorder**
DAVID L. FOGELSON, MD

522 **Brain Imaging and Neurodevelopmental Psychiatry**
ROBERT L. HENDREN, DO

523 **Treating Compulsive Behaviors in Dermatology**
JOHN Y. M. KOO, MD

523 **Bulimia Nervosa**
JOEL YAGER, MD

ALERTS, NOTICES, AND CASE REPORTS

525 **Aspergillar Myocarditis and Acute Coronary Artery Occlusion in an Immunocompromised Patient**
MICHAEL K. HORI, MD; LAWRENCE L. KNIGHT, MD; PAULA G. CARVALHO, MD; and DENNIS L. STEVENS, MD

From the Department of Medicine, University of California, Davis; the Department of Medicine, University of Washington School of Medicine, Seattle; and the Departments of Medicine and Pathology, Veterans Affairs Medical Center, Boise, Idaho.

527 **Bilateral Spontaneous Renal Hemorrhage Due to Polyarteritis Nodosa**
JOSEPH C. PRESTI, Jr, MD, and PETER R. CARROLL, MD

From the Department of Urology, University of California, San Francisco, School of Medicine. Dr Presti is now with the Memorial Sloan-Kettering Cancer Center, New York, New York.

528 **The Numb Chin in Metastatic Cancer**
CHERYL P. HARRIS, MD, and J. RICHARD BARINGER, MD

From the Departments of Pathology and Neurology, University of Utah Medical Center, Salt Lake City.

531 **Massive Splenic Infarction in Doubly Abnormal Heterozygous Sickling Disorders—A New Complication of Acute Splenic Sequestration Syndrome**
ROY A. BERRY, MD; ELIZABETH A. ODUMAKINDE, MD; and JERRY P. LEWIS, MD

From the Department of Internal Medicine and the Division of Hematology and Oncology, Department of Pathology, University of California, Davis, Medical Center, Sacramento.

COMMENTARY

533 **Managed-Care Plans—Their Future Under National Health Insurance**
THOMAS P. WEIL, PhD

From the Bedford Health Associates, Asheville, North Carolina.

538 **Physician, Heal Thy Planet**
WILLIAM B. STEWART, MD

Dr Stewart is the Executive Director, Program in Medicine and Philosophy, California Pacific Medical Center, San Francisco, and is in private practice.

EDITORIALS

540 **There's a Long, Long Trail A-winding . . .**

540 **Physicians and the Human Immunodeficiency Virus**
PAUL A. VOLBERDING, MD

Dr Volberding is Professor of Medicine, University of California, San Francisco, School of Medicine, and Director, AIDS Program, San Francisco General Hospital Medical Center, San Francisco.

(Continued on Page 458)

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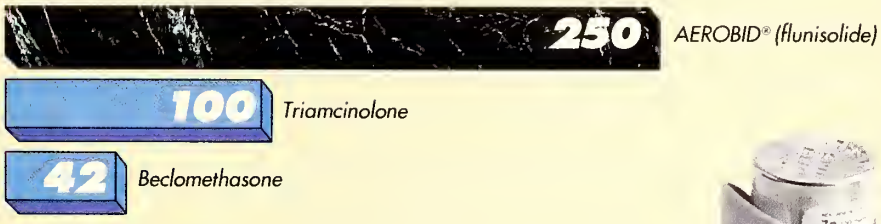

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CONTRAINDICATIONS

AeroBid Inhaler is contraindicated in the primary treatment of status asthmaticus or other acute episodes of asthma where intensive measures are required

Hypersensitivity to any of the ingredients of this preparation contraindicates its use

WARNINGS

Particular care is needed in patients who are transferred from systemically active corticosteroids to AeroBid Inhaler because deaths due to adrenal insufficiency have occurred in asthmatic patients during and after transfer from systemic corticosteroids to aerosol corticosteroids After withdrawal from systemic corticosteroids, a number of months are required for recovery of hypothalamic-pituitary-adrenal (HPA) function During this period of HPA suppression, patients may exhibit signs and symptoms of adrenal insufficiency when exposed to trauma, surgery or infections, particularly gastroenteritis Although AeroBid Inhaler may provide control of asthmatic symptoms during these episodes, it does NOT provide the systemic steroid that is necessary for coping with these emergencies.

During periods of stress or a severe asthmatic attack, patients who have been withdrawn from systemic corticosteroids should be instructed to resume systemic steroids (in large doses) immediately and to contact their physician for further instruction These patients should also be instructed to carry a warning card indicating that they may need supplementary systemic steroids during periods of stress or severe asthma attack To assess the risk of adrenal insufficiency in emergency situations, routine tests of adrenal cortical function, including measurement of early morning resting cortisol levels, should be performed periodically in all patients An early morning resting cortisol level may be accepted as normal if it falls at or near the normal mean level

Localized infections with Candida albicans or Aspergillus niger have occurred in the mouth and pharynx and occasionally in the larynx Positive cultures for oral Candida may be present in up to 34% of patients Although the frequency of clinically apparent infection is considerably lower, these infections may require treatment with appropriate antifungal therapy or discontinuance with AeroBid Inhaler

AeroBid Inhaler is not to be regarded as a bronchodilator and is not indicated for rapid relief of bronchospasm

Patients should be instructed to contact their physician immediately when episodes of asthma that are not responsive to bronchodilators occur during the course of treatment During such episodes, patients may require therapy with systemic corticosteroids

There is no evidence that control of asthma can be achieved by administration of the drug in amounts greater than the recommended doses, which appear to be the therapeutic equivalent of approximately 10 mg/day of oral prednisone Theoretically, the use of inhaled corticosteroids with alternate day prednisone systemic treatment should be accompanied by more HPA suppression than a therapeutically equivalent regimen of either alone

Transfer of patients from systemic steroid therapy to AeroBid Inhaler may unmask allergic conditions previously suppressed by the systemic steroid therapy, e g , rhinitis, conjunctivitis, and eczema

PRECAUTIONS

General: Because of the relatively high molar dose of flunisolide per activation in this preparation, and because of the evidence suggesting higher levels of systemic absorption with flunisolide than with other comparable inhaled corticosteroids, patients treated with AeroBid should be observed carefully for any evidence of systemic corticosteroid effect, including suppression of bone growth in children Particular care should be taken in observing patients post-operatively or during periods of stress for evidence of a decrease in adrenal function During withdrawal from oral steroids, some patients may experience symptoms of systemically active steroid withdrawal, e g , joint and/or muscular pain, lassitude and depression, despite maintenance or even improvement of respiratory function

In responsive patients, flunisolide may permit control of asthmatic symptoms without suppression of HPA function Since flunisolide is absorbed into the circulation and can be systemically active, the beneficial effects of AeroBid Inhaler in minimizing or preventing HPA dysfunction may be expected only when recommended dosages are not exceeded.

The long-term effects of the drug in human subjects are still unknown. In particular, the local effects of the agent on developmental or immunologic processes in the mouth, pharynx, trachea, and lung are unknown There is also no information about the possible long-term systemic effects of the agent.

The potential effects of the drug on acute, recurrent, or chronic pulmonary infections, including active or quiescent tuberculosis, are not known Similarly, the potential effects of long-term administration of the drug on lung or other tissues are unknown

Pulmonary infiltrates with eosinophilia may occur in patients on AeroBid Inhaler therapy Although it is possible that in some patients this state may become manifest because of systemic steroid withdrawal when inhalational steroids are administered, a causative role for the drug and/or its vehicle cannot be ruled out.

Carcinogenesis: A 22-month study was conducted in Swiss derived mice to evaluate the carcinogenic potential of the drug There was an increase in the incidence of pulmonary adenomas within the range of adenomas previously reported in the literature for untreated or control Swiss derived mice An additional study is being conducted in a species with a lower incidence of spontaneous pulmonary tumors

Impairment of fertility: Female rats receiving high doses of flunisolide (200 mcg/kg/day) showed some evidence of impaired fertility Reproductive performance in the low (8 mcg/kg/day) and mid-dose (40 mcg/kg/day) groups was comparable to controls

Pregnancy: Pregnancy Category C As with other corticosteroids, flunisolide has been shown to be teratogenic in rabbits and rats at doses of 40 and 200 mcg/kg/day respectively It was also fetotoxic in these animal reproductive studies There are no adequate and well-controlled studies in pregnant women Flunisolide should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether this drug is excreted in human milk Because other corticosteroids are excreted in human milk, caution should be exercised when flunisolide is administered to nursing women

ADVERSE REACTIONS

Adverse events reported in controlled clinical trials and long-term open studies in 514 patients treated with AeroBid are described below Of those patients, 463 were treated for 3 months or longer, 407 for 6 months or longer, 287 for 1 year or longer, and 122 for 2 years or longer

Musculoskeletal reactions were reported in 35% of steroid-dependent patients in whom the dose of oral steroid was being tapered This is a well-known effect of steroid withdrawal

Incidence 10% or greater

Gastrointestinal diarrhea (10%), nausea and/or vomiting (25%), upset stomach (10%); *General* flu (10%), *Mouth and Throat* sore throat (20%), *Nervous System* headache (25%), *Respiratory* cold symptoms (15%), nasal congestion (15%), upper respiratory infection (25%), *Special Senses*: unpleasant taste (10%)

Incidence 3-9%

Cardiovascular palpitations, *Gastrointestinal*, abdominal pain, heartburn, *General*, chest pain, decreased appetite, edema, fever, *Mouth and Throat* Candida infection, *Nervous System* dizziness, irritability, nervousness, shakiness, *Reproductive*, menstrual disturbances, *Respiratory* chest congestion, cough,* hoarseness, rhinitis, runny nose, sinus congestion, sinus drainage, sinus infection, sinusitis, sneezing, sputum, wheezing*, *Skin* eczema, itching (pruritus), rash, *Special Senses*, ear infection, loss of smell or taste

Incidence 1-3%

General chills, increased appetite and weight gain, malaise, peripheral edema, sweating, weakness, *Cardiovascular* hypertension, tachycardia, *Gastrointestinal* constipation, dyspepsia, gas, *Hemic/Lymph* capillary fragility, enlarged lymph nodes, *Mouth and Throat* dry throat, glossitis, mouth irritation, pharyngitis, phlegm, throat irritation, *Nervous System* anxiety, depression, faintness, fatigue, hyperactivity, hypoactivity, insomnia, moodiness, numbness, vertigo, *Respiratory* bronchitis, chest tightness,* dyspnea, epistaxis, head stuffiness, laryngitis, nasal irritation, pleurisy, pneumonia, sinus discomfort, *Skin* acne, hives, or urticaria, *Special Senses* blurred vision, earache, eye discomfort, eye infection.

Incidences less than 1%, judged by investigators as possibly or probably drug-related abdominal fullness, shortness of breath

*The incidences as shown of cough, wheezing, and chest tightness were judged by investigators to be possibly or probably drug-related In placebo-controlled trials, the overall incidences of these adverse events (regardless of investigators' judgement of drug relationship) were similar for drug and placebo-treated groups They may be related to the vehicle or delivery system

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References:

1 *National Heart, Lung, and Blood Institute National Asthma Education Program Expert Panel Report – Guidelines for the Diagnosis and Management of Asthma* Bethesda, Md US Dept of Health and Human Services, 1991

2 *Physicians' Desk Reference*® 45th ed Oradell NJ Medical Economics Co Inc, 1991 955, 1862, 2026

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ABSTRACTS NOVEMBER 1991

(Riley K, Myers W, Schneeweiss R: Recruiting physicians to rural practice—Suggestions for success. West J Med 1991 Nov; 155:500-504)

Medical school graduates from 1986 to 1988 and current residents in 12 family practice residency programs in the Northwest (N = 302) were surveyed to identify important factors in the recruitment process for their first postresidency placement. The study sought to compare the recruitment practices of rural communities and urban sites. Specific questions addressed in the study concerned sources of information about practice opportunities, stage in training when job search was initiated, factors related to unsuccessful site visits, and activities scheduled in the visit. Results indicated that referrals from faculty were the most valued source of information. Most job searches were initiated in the first 6 months of the third year in training. An unreceptive physician community and a reluctant spouse or partner were substantial problems for residents making site visits to rural communities. Rural sites tended to provide a broader mix of professional and personal activities during the visit.

PHYSICIAN RECRUITMENT
URBAN VERSUS RURAL PRACTICE
RURAL PHYSICIAN RECRUITING

(Riley K, Myers W, Schneeweiss R: Recruiting physicians to rural practice—Suggestions for success. West J Med 1991 Nov; 155:500-504)

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(Continued from Page 453)

541 **Liver Transplantation—Challenges for the Future**
EMMET B. KEEFFE, MD
Dr Keeffe is Professor of Medicine, Division of Gastroenterology, Oregon Health Sciences University, Portland, Oregon.

544 **Molecular Genetics in the Cancer Clinic**
ERIC H. RADANY, MD, PhD
From the Department of Radiation Oncology and the G. W. Hooper Research Foundation, University of California, San Francisco.

CORRESPONDENCE

547 **Human Immunodeficiency Virus Infection in Children Who Received Transfusions in Mexico**
RONALD M. FERDMAN, MD; JOSEPH A. CHURCH, MD; LAURENE MASCOLA, MD; and JUDITH K. SATO, MD

548 **Toxic Exposure to Betamix**
MARC TUNZI, MD

548 **Smoking Cessation Attitudes, Practices, and Policies Among California Primary Care Physicians**
RUSSELL L. YOUNG, PhD; CATHERINE CROOKS, PhD; JOHN P. ELDER, PhD, MPH; ERIN KENNEY, PhD, MPH; DILEEP G. BAL, MD; and MICHAEL JOHNSON, PhD

549 **An Inexpensive, Convenient Adjunct for the Treatment of Diabetes**
GARY W. EVANS, PhD

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LESSONS FROM THE PRACTICE

551 **My Jogging Partner**
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553 **Heart and Mind**
MARSHALL H. CHIN, MD
Dr Chin is a medical resident at the Brigham and Women's Hospital, Boston, Massachusetts.

SPECIAL ARTICLE

555 **Memoirs of an Amnesiac—Two Years With Brain Cancer, or the Outer Space of Living With Brain Tumors**
ALEXANDRA DANE DOR-NER

OTHER FEATURES

461 **In Memoriam**
464 **Continuing Medical Education Activities in Arizona; California, Hawaii, and Nevada; Colorado; Idaho; New Mexico; Utah; Washington**
474 **Subscription Information**
563 **Instructions for Authors**
564 **Classified Advertising**
576 **Western State Medical Associations' Meetings**
Poems: 504, 537, 539

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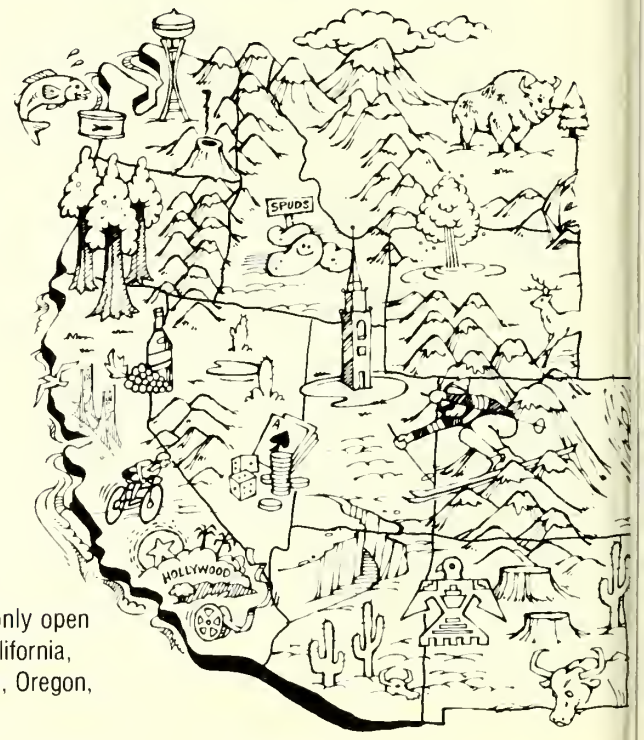

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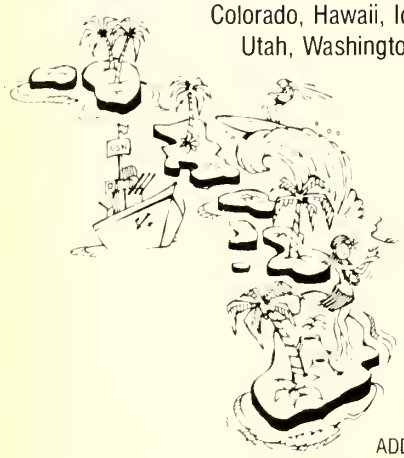

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BARTLETT, JOHN C., Orinda. Died Jun 13, 1991, aged 84. Graduate of University of Southern California, Los Angeles, 1937. Licensed in California in 1937. Dr Bartlett was a member of the Alameda-Contra Costa Medical Association.

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BERTERO, JULES, Santa Maria. Died Apr 19, 1991, aged 89. Graduate of St Louis University, Missouri, 1929. Licensed in California in 1930. Dr Bertero was a member of the Santa Barbara County Medical Society.

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BESCOBY, FELIX J., Upland. Died Jul 11, 1991, aged 68. Graduate of Northwestern University Medical School, Chicago, 1949. Licensed in California in 1949. Dr Bescoby was a member of the San Bernardino County Medical Society.

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BOOMER, JOSEPH M., Richmond. Died May 12, 1991, aged 81. Graduate of University of Nebraska, Omaha, 1934. Dr Boomer was a member of the Alameda-Contra Costa Medical Association.

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GULL, REUBEN, Chino. Died Apr 21, 1991, aged 67. Graduate of University of Minnesota Medical School, Minneapolis, 1947. Licensed in California in 1949. Dr Gull was a member of the San Bernardino County Medical Society.

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KOCH, FREMONT P., Camarillo. Died Sep 27, 1991, aged 72. Graduate of Washington University, St Louis, Missouri. Dr Koch was a member of the Ventura County Medical Society.

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MASSENGILL, JAMES B., Ukiah. Died Jul 1, 1991, aged 76. Graduate of University of Tennessee, Memphis, 1937. Licensed in California in 1946. Dr Massengill was a member of the Mendocino-Lake County Medical Society.

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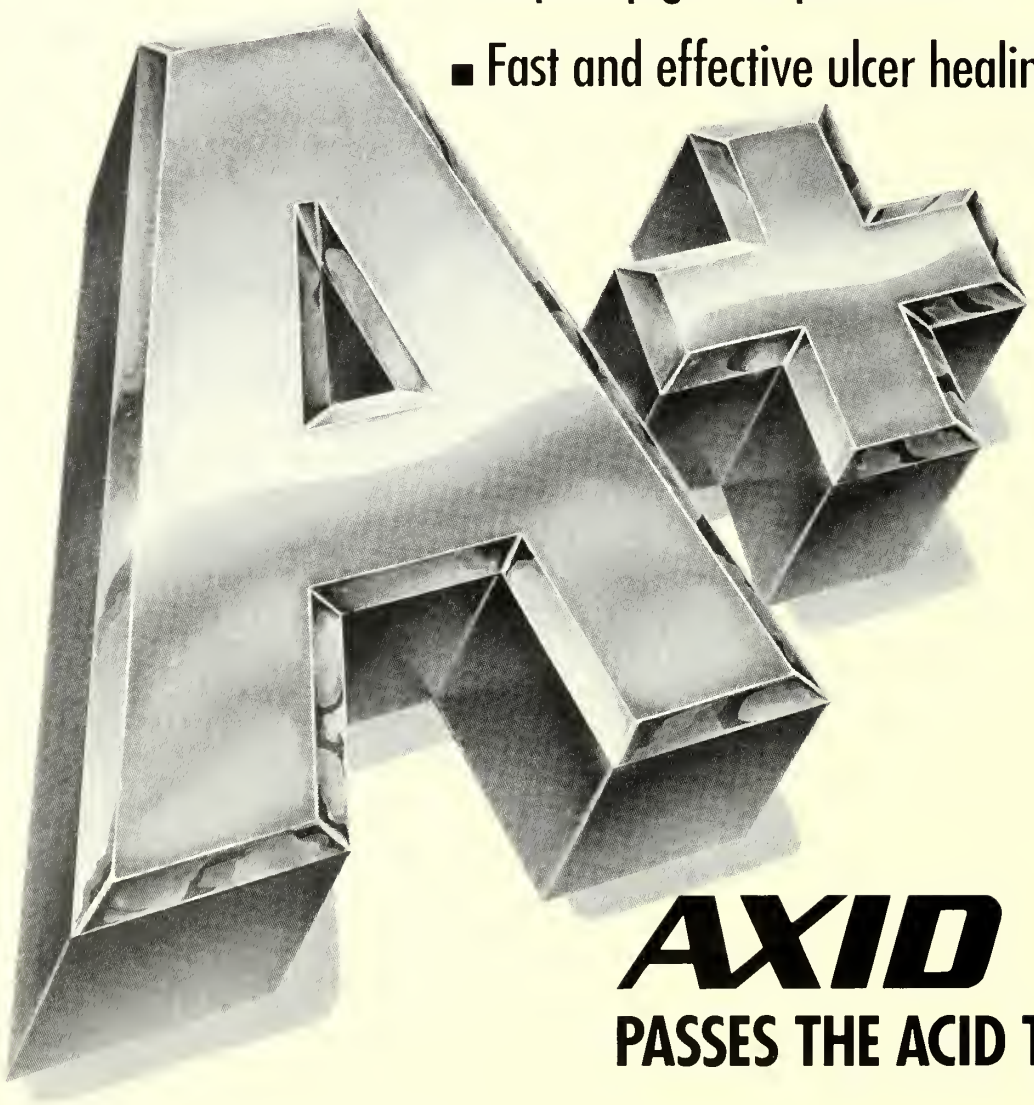

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Brief Summary. Consult the package insert for complete prescribing information.
Indications and Usage: 1. *Active duodenal ulcer*—for up to 8 weeks of treatment. Most patients heal within 4 weeks.

2. *Maintenance therapy*—for healed duodenal ulcer patients at a reduced dosage of 150 mg h.s. The consequences of therapy with Axid for longer than 1 year are not known.

Contraindications: Known hypersensitivity to the drug. Because cross sensitivity in this class of compounds has been observed, H_2-receptor antagonists, including Axid, should not be administered to patients with a history of hypersensitivity to other H_2-receptor antagonists.

Precautions: *General*—1. Symptomatic response to nizatidine therapy does not preclude the presence of gastric malignancy.

2. Dosage should be reduced in patients with moderate to severe renal insufficiency.

3. In patients with normal renal function and uncomplicated hepatic dysfunction, the disposition of nizatidine is similar to that in normal subjects.

Laboratory Tests—False-positive tests for urobilinogen with Multistix® may occur during therapy.

Drug Interactions—No interactions have been observed with theophylline, chlordiazepoxide, lorazepam, lidocaine, phenytoin, and warfarin. Axid does not inhibit the cytochrome P-450 enzyme system, therefore, drug interactions mediated by inhibition of hepatic metabolism are not expected to occur. In patients given very high doses (3,900 mg) of aspirin daily, increased serum salicylate levels were seen when nizatidine, 150 mg b.i.d., was administered concurrently.

Carcinogenesis, Mutagenesis, Impairment of Fertility—A 2-year oral carcinogenicity study in rats with doses as high as 500 mg/kg/day (about 80 times the recommended daily therapeutic dose) showed no evidence of a carcinogenic effect. There was a dose-related increase in the density of enterochromaffin-like (ECL) cells in the gastric oxyntic mucosa. In a 2-year study in mice, there was no evidence of a carcinogenic effect in male mice, although hyperplastic nodules of the liver were increased in the high-dose males as compared with placebo. Female mice given the high dose of Axid (2,000 mg/kg/day, about 330 times the human dose) showed marginally statistically significant increases in hepatic carcinoma and hepatic nodular hyperplasia with no numerical increase seen in any of the other dose groups. The rate of hepatic carcinoma in the high-dose animals was within the historical control limits seen for the strain of mice used. The female mice were given a dose larger than the maximum tolerated dose, as indicated by excessive (30%) weight decrement as compared with concurrent controls and evidence of mild liver injury (transaminase elevations). The occurrence of a marginal finding at high dose only in animals given an excessive and somewhat hepatotoxic dose, with no evidence of a carcinogenic effect in rats, male mice, and female mice (given up to 360 mg/kg/day, about 60 times the human dose), and a negative mutagenicity battery are not considered evidence of a carcinogenic potential for Axid.

Axid was not mutagenic in a battery of tests performed to evaluate its potential genetic toxicity, including bacterial mutation tests, unscheduled DNA synthesis, sister chromatid exchange, mouse lymphoma assay, chromosome aberration tests, and a micronucleus test.

In a 2-generation, perinatal and postnatal fertility study in rats, doses of nizatidine up to 650 mg/kg/day produced no adverse effects on the reproductive performance of parental animals or their progeny.

Pregnancy—Teratogenic Effects—Pregnancy Category C—Oral reproduction studies in rats at doses up to 300 times the human dose and in Dutch Belted rabbits at doses up to 55 times the human dose revealed no evidence of impaired fertility or teratogenic effect; but, at a dose equivalent to 300 times the human dose, treated rabbits had abortions, decreased number of live fetuses, and depressed fetal weights. On intravenous administration to pregnant New Zealand White rabbits, nizatidine at 20 mg/kg produced cardiac enlargement, coarctation of the aortic arch, and cutaneous edema in 1 fetus, and at 50 mg/kg, it produced ventricular anomaly, distended abdomen, spina bifida, hydrocephaly, and enlarged heart in 1 fetus. There are, however, no adequate and well-controlled studies in pregnant women. It is also not known whether nizatidine can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Nizatidine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers—Studies in lactating women have shown that 0.1% of an oral dose is secreted in human milk in proportion to plasma concentrations. Because of growth depression in pups reared by treated lactating rats, a decision should be made whether to discontinue nursing or the drug, taking into account the importance of the drug to the mother.

Pediatric Use—Safety and effectiveness in children have not been established.

Use in Elderly Patients—Healing rates in elderly patients were similar to those in younger age groups as were the rates of adverse events and laboratory test abnormalities. Age alone may not be an important factor in the disposition of nizatidine. Elderly patients may have reduced renal function.

Adverse Reactions: Clinical trials of varying durations included almost 5,000 patients. Among the more common adverse events in domestic placebo-controlled trials of over 1,900 nizatidine patients and over 1,300 on placebo, sweating (1% vs 0.2%), urticaria (0.5% vs <0.01%), and somnolence (2.4% vs 1.3%) were significantly more common with nizatidine. It was not possible to determine whether a variety of less common events were due to the drug.

Hepatic—Hepatocellular injury (elevated liver enzyme tests or alkaline phosphatase) possibly or probably related to nizatidine occurred in some patients. In some cases, there was marked elevation (>500 IU/L) in SGOT or SGPT and, in a single instance, SGPT was >2,000 IU/L. The incidence of elevated liver enzymes overall and elevations of up to 3 times the upper limit of normal, however, did not significantly differ from that in placebo patients. All abnormalities were reversible after discontinuation of Axid. Since market introduction, hepatitis and jaundice have been reported. Rare cases of cholestatic or mixed hepatocellular and cholestatic injury with jaundice have been reported with reversal of the abnormalities after discontinuation of Axid.

Cardiovascular—In clinical pharmacology studies, short episodes of asymptomatic ventricular tachycardia occurred in 2 individuals administered Axid and in 3 untreated subjects.

CNS—Rare cases of reversible mental confusion have been reported.

Endocrine—Clinical pharmacology studies and controlled clinical trials showed no evidence of antiandrogenic activity due to nizatidine. Impotence and decreased libido were reported with equal frequency by patients on nizatidine and those on placebo. Gynecomastia has been reported rarely.

Hematologic—Fatal thrombocytopenia was reported in a patient treated with nizatidine and another H_2-receptor antagonist. This patient had previously experienced thrombocytopenia while taking other drugs. Rare cases of thrombocytopenic purpura have been reported.

Integumental—Sweating and urticaria were reported significantly more frequently in nizatidine- than in placebo-treated patients. Rash and exfoliative dermatitis were also reported.

Hypersensitivity—As with other H_2-receptor antagonists, rare cases of anaphylaxis following nizatidine administration have been reported. Rare episodes of hypersensitivity reactions (eg, bronchospasm, laryngeal edema, rash, and eosinophilia) have been reported.

Other—Hyperuricemia unassociated with gout or nephrolithiasis was reported. Eosinophilia, fever, and nausea related to nizatidine have been reported.

Overdosage: Overdoses of Axid have been reported rarely. If overdosage occurs, activated charcoal, emesis, or lavage should be considered along with clinical monitoring and supportive therapy. Renal dialysis does not substantially increase clearance of nizatidine due to its large volume of distribution.

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References
1. Data on file, Lilly Research Laboratories
2. *Scand J Gastroenterol* 1987;22(suppl 136):61-70
3. *Scand J Gastroenterol* 1987;22(suppl 136):47-55
4. *Am J Gastroenterol* 1989;84:769-774

NZ-2943-B-149347

Additional information available to the profession on request

Lilly

Eli Lilly and Company
Indianapolis, Indiana
46285

In Memoriam

(Continued from Page 461)

MEADOR, JAMES H., San Diego. Died Sep 1, 1991, aged 76. Graduate of University of Arizona, Tucson, 1939. Dr Meador was a member of the San Diego County Medical Society.

❧

MENDA, KISHEN B., Arcata. Died Jul 11, 1991, aged 48. Graduate of G. S. Medical College, India. Dr Menda was a member of the Humboldt-Del Norte Medical Society.

❧

MERRILL, ROBERT L., Hemet. Died Aug 31, 1991, aged 78. Graduate of Washington University, St Louis, Missouri, 1940. Licensed in California in 1946. Dr Merrill was a member of the Riverside County Medical Association.

❧

NESSELROD, JERROLD PEERMAN, Santa Barbara. Died Sep 6, 1991, aged 87. Graduate of Northwestern University, Chicago, Illinois, 1930. Licensed in California in 1947. Dr Nesselrod was a member of the Santa Barbara County Medical Society.

❧

PECK, SAMUEL G., San Diego. Died Sep 1, 1991, aged 82. Graduate of St Louis University, Missouri, 1936. Dr Peck was a member of the San Diego County Medical Society.

❧

PHILLIPS, R. E., Visalia. Died Jul 19, 1991, aged 59. Graduate of University of Rochester, New York, 1958. Licensed in California in 1960. Dr Phillips was a member of the Tulare County Medical Society.

❧

POTTER, GEORGE V., Walnut Creek. Died Jul 13, 1991, aged 78. Graduate of University of Illinois, Chicago, 1938. Dr Potter was a member of the Alameda-Contra Costa Medical Association.

❧

RAY, LEIGHTON W., Santa Rosa. Died Jul 28, 1991, aged 93. Graduate of Harvard Medical School, Boston, Massachusetts, 1924. Dr Ray was a member of the Sonoma County Medical Association.

RICHMOND, ROBERT A., Bakersfield. Died Aug 18, 1991, aged 70. Graduate of New York Medical College, 1949. Licensed in California in 1955. Dr Richmond was a member of the Kern County Medical Society.

❧

SPAUR, R. CRAIG, Riverside. Died Jun 8, 1991, aged 42. Graduate of University of Nebraska College of Medicine, 1980. Licensed in California in 1986. Dr Spaur was a member of the Riverside County Medical Association.

Denver Medical Society

BLANEY, LOREN F. Died Aug 14, 1991, aged 78. Graduate of Washington University, St Louis, Missouri, 1938. Licensed in Colorado in 1951.

❧

LUBCHENCO, MICHAEL A. Died Aug 11, 1991, aged 71. Graduate of University of Colorado Health Sciences Center, Denver, 1945. Licensed in Colorado in 1946.

❧

SCHONEBAUM, ROBERT M. Died Jul 17, 1991, aged 69. Graduate of Creighton University School of Medicine, Omaha, Nebraska, 1945. Licensed in Colorado in 1945.

Idaho Medical Association

GOATES, GREGORY L., Blackfoot. Died Jul 26, 1991, aged 45. Graduate of University of Utah Medical School, Salt Lake City, 1972. Licensed in Idaho in 1985. Dr Goates was a member of the Bingham County Medical Society.

❧

WEHLER, ANDREW J., Riggins. Died Aug 26, 1991, aged 72. Graduate of Jefferson Medical School, Philadelphia, Pennsylvania, 1947. Licensed in Idaho in 1987.

New Mexico Medical Society

GUTOWSKI, FRANZ, Tucumcari. Died Aug 4, 1991, aged 50. Graduate of Dnepropebrowsky Medical Institute, 1938. Licensed in New Mexico in 1969. Dr Gutowski was a member of the Quay County Medical Society.

❧

SPINING, WILLIAM D., Santa Fe. Died Jun 23, 1991, aged 83. Graduate of University of California, 1937. Licensed in New Mexico in 1968. Dr Spining was a member of the Santa Fe County Medical Society.

Continuing Medical Education

ARIZONA • CALIFORNIA, HAWAII, NEVADA • COLORADO • IDAHO • NEW MEXICO • UTAH • WASHINGTON

ARIZONA

The following list of continuing medical education programs in Arizona is compiled by the Arizona Medical Association. All courses listed have been certified as meeting the criteria for Category I of the ArMA CME Certificate and the AMA Physicians Recognition Award. To list Category I continuing medical education programs, please send information to Arizona Medical Association, 810 West Bethany Home Road, Phoenix, AZ 85013; or phone (602) 246-8901.

Brochures and registration forms are available from the contact person or organization sponsoring the program.

November 14-16—**Fourth Annual Spine Workshop.** Barrow's Neurological Institute, St Joseph's Hospital and Medical Center at Marriott's Mountain Shadows Resort, Scottsdale. Wed-Fri. Contact: Toby Anchie, (602) 285-3178 or (800) BARROW-1.

November 15-16—**Pediatric Genetics and Dermatology: A Practical Approach.** University of Arizona College of Medicine at Hotel Park Tucson. Fri-Sat. Contact: (602) 626-7832.

November 15-16—**4th Annual Techniques in Gynecological Surgery.** Mayo Clinic-Scottsdale at the Scottsdale Plaza Resort, Scottsdale. Fri-Sat. Contact: Trish Gean, Mayo Clinic-Scottsdale.

November 15-17—**The Advanced Medical Staff Seminar.** Joint Commission on the Accreditation of Health Care Organizations, Phoenix. Fri-Sun. Contact: Kyle Dooley Kinder, ArHA, (602) 968-1083.

November 22—**Update on Arthritis.** University of Arizona College of Medicine at the Sheraton Conquistador, Tucson. Fri. Contact: U of A.

November 24-27—**8th Annual "State of the Art in Total Joint Replacement."** Harrington Arthritis Research Center, St Luke's Hospital at the Scottsdale Princess Resort, Scottsdale. Sun-Wed. Contact: Nancy Neroni, (602) 254-0377.

CONTACT INFORMATION

ArMA—Contact: Arizona Medical Association, 810 W Bethany Home Rd, Phoenix, AZ 85013 (602) 246-8901

Mayo Clinic-Scottsdale—Contact: Jodi Lee Smith, Postgraduate Courses, Mayo Clinic-Scottsdale, (602) 391-8300.

U of A—Contact: University of Arizona College of Medicine, Arizona Health Sciences Center, Tucson, AZ 85724 (602) 626-7832.

CALIFORNIA, HAWAII, AND NEVADA

This listing of continuing education programs in California, Hawaii, and Nevada is supplied by the Committee on Continuing Medical Education of the California Medical Association. All courses and meetings listed have been approved for Category I credit toward the CMA Certificate in Continuing Medical Education. To have accredited courses listed here, please send information at least two months in advance to Department of Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690; or phone (415) 541-0900. For more information on accreditation or certification, please write to the above address.

ALLERGY

February 6-8—**Allergy Diagnosis.** UCSD at La Jolla Village Inn. Thurs-Sat. 20 hrs. $290. Contact: Janice Turner, PO Box 2586, La Jolla 92038. (619) 459-1564

March 27-28—**Asthma and Allergy in the 1990s.** Medical Education Resources at Wyndham Hotel, Palm Springs. Fri-Sat. Contact: MER, 1500 W Canal Ct, Ste 500, Littleton, CO 80120. (800) 421-3756.

ANESTHESIOLOGY

January 9-12—**UCSD Anesthesia Update: 1992.** UCSD at Hotel del Coronado, San Diego. Thurs-Sun. Contact: UCSD.

January 19-21—**Second America-Japan Anesthesia Congress.** International Anesthesia Research Society at Sheraton Waikiki Hotel, Honolulu, Hawaii. Sun-Tue. 14 hrs. $250. Contact: Vicky Larsen, University of Utah School of Medicine, 50 North Medical Drive, Salt Lake City, UT 84132. (801) 581-6115.

January 19-24—**Hawaiian Seminar on Clinical Anesthesia.** California Society of Anesthesiologists at Westin Maui Hotel, Kaanapali Beach, Maui, Hawaii. Sun-Fri. 20 hrs. Contact: California Society of Anesthesiologists, 1065 E Hillsdale Blvd, #410, Foster City 94404. (800) 345-3691.

January 24-26—**30th Clinical Conference in Pediatric Anesthesiology.** Children's Hospital of Los Angeles at Stouffer Concourse Hotel. Fri-Sun. 15 hrs. Contact: Katherine Barky, MD, PO Box 54700, Los Angeles 90054. (213) 669-2262.

March 13-17—**66th Congress of the International Anesthesia Research Society.** International Anesthesia Research Society at San Francisco Hilton & Towers. Fri-Tues. Contact: Anne Maggiore, IARS, 2 Summit Park Dr, Ste 140, Cleveland, OH 44131. (216) 642-1124.

March 21-22—**Postgraduate Assembly.** Los Angeles County Society of Anesthesiologists at Sheraton Universal Hotel, Universal City. Sat-Sun. Contact: Michael Carlson, 1903 Redondo Ave, Long Beach 90804. (213) 597-2661.

March 21-26—**20th Obstetric Anesthesia Conference.** Ohio State University Hospitals at Sheraton Waikiki Hotel, Honolulu, Hawaii. Sat-Thurs. Contact: Arlene Rogers, 410 W 10th Ave, Columbus, OH 43210. (614) 293-8487.

CARDIOLOGY

November 15-16—**The Cardiac Patient.** Memorial/UCI Center for Health Education at Marriott, Newport Beach. Fri-Sat. Contact: UCI.

December 7—**9th Annual International Pulmonary Symposium.** Memorial/UCI Center for Health Education. Sat. Contact: UCI.

February 14-16—**Arrhythmias: Interpretation, Diagnosis and Management.** Medical Education Resources at Disneyland Hotel, Anaheim. Fri-Sun. Contact: MER, 1500 W Canal Ct, Ste 500, Littleton, CO 80120. (800) 421-3756.

March 20-21—**Cardiac Diagnostic Methods & Risk Management.** Medical Education Resources at Caesars Palace, Las Vegas, Nevada. Fri-Sat. Contact: MER, 1500 W Canal Ct, Ste 500, Littleton, CO 80120. (800) 421-3756.

April 4—**Practical Cardiology for the '90s.** Grossmont Hospital at La Mesa. Sat. Contact: Karen Hamilton, PO Box 158, La Mesa 91944-0158. (619) 589-4168.

April 6-11—**31st Annual Cardiology Retreat.** Scripps Clinic and Research Foundation at Rancho Santa Fe. Mon-Sat. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

April 21-23—**2nd Annual Symposium on Coronary Stenting: A Live Demonstration Course.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Tues-Thurs. 18 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

CRITICAL CARE

January 9-11—**The California Trauma Conference.** UCD at Hyatt Regency Hotel, Sacramento. Thurs-Sat. 14 hrs. $395. Contact: UCD.

DERMATOLOGY

January 17-19—**Practical Dermatology and Dermatologic Office Procedures for the Primary Care Physician.** UCSD at Hyatt Regency, La Jolla. Fri-Sun. 20 hrs. Contact: Jacqueline Shiller, Box 84296, San Diego 92138. (619) 223-2997.

January 31-February 2—**Cutaneous Malignancies: 1992 Skin Cancer Update.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Fri-Sun. 18 hrs. Contact: Susan Buntjer, Scripps Clinic and Research Foundation, 10666 N Torrey Pines Road, La Jolla 92037. (619) 554-8556.

February 27—**Problems of the Aging Skin.** Stanford Medical Center at Palm Springs. Thurs-Sun. Contact: Pamela Bain, R-144, Stanford 94305. (415) 723-7854.

(Continued on Page 466)

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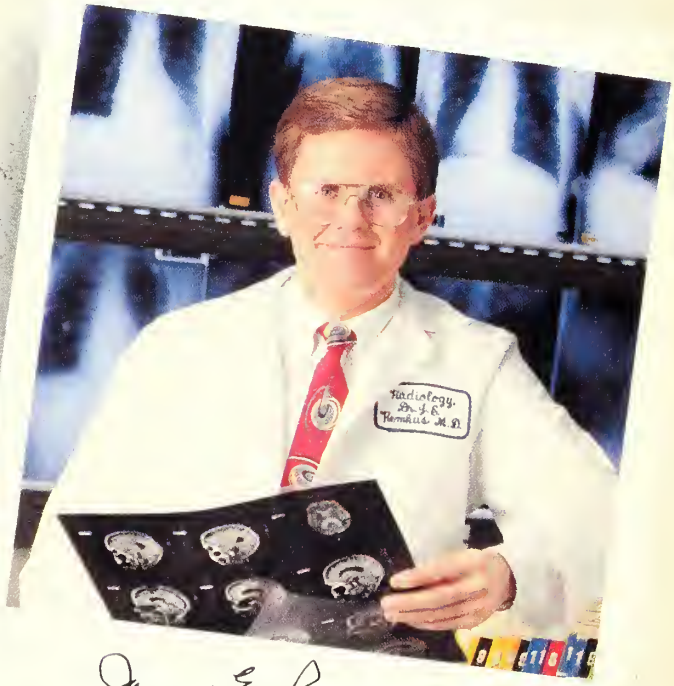

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CONTINUING MEDICAL EDUCATION

(Continued from Page 464)

EMERGENCY MEDICINE

November 16-17—**Biomechanics of Trauma.** UCSD at San Diego Marriott. Sat-Sun. Contact: UCSD.

December 9-13—**Emergency Medicine Symposia II.** UCSD at Basic Science Building, La Jolla. Mon-Fri. Contact: UCSD.

January 10-11—**California Trauma Conference.** UCD at Hyatt Regency, Sacramento. Fri-Sat. Contact: UCD.

January 13-17—**Emergency Medicine Symposia I.** UCSD at San Diego Hilton Beach & Tennis Resort. Mon-Fri. Contact: UCSD.

February 23-28—**Emergency Medicine.** UCD at Incline Village, Nevada. Sun-Fri. Contact: UCD.

March 8-13—**13th Annual Mammoth Mountain Emergency Medicine Ski Conference.** CAL/ACEP and Orange County Emergency Department at Mammoth Lakes. Sun-Fri. 18 hrs. $395. Contact: Mark Song, Medical Conferences, PO Box 52-B, Newport Beach 92662. (714) 552-0831.

April 1-4—**8th Annual Advances in Emergency Medicine.** UCSF at Pan Pacific Hotel, San Francisco. Wed-Sat. $455. Contact: UCSF.

ENDOCRINOLOGY AND METABOLISM

March 4-5—**Advances in Endocrinology and Metabolism.** UCSF at Pan Pacific Hotel, San Francisco. Wed-Thurs. 14.5 hrs. $295. Contact: UCSF.

March 6—**18th Annual Diabetes Symposium.** UCD at Sacramento. Fri. 6 hrs. $140. Contact: UCD.

March 6-7—**Diabetes Update.** UCSF at Pan Pacific Hotel, San Francisco. Fri-Sat. 10 hrs. $245. Contact: UCSF.

FAMILY PRACTICE/PRIMARY CARE

November 15-17—**Family Practice Today & Tomorrow.** UCSD at Sheraton Hotel, San Diego. Fri-Sun. Contact: UCSD.

KEY TO ABBREVIATIONS

CMA — California Medical Association
Contact: Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690. (415) 541-0900.

DREW — Charles R. Drew Postgraduate Medical School
Contact: Herbert M. Thomas, MD, MPH, Director of CME, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th St, Los Angeles 90059. (213) 603-3183.

LLU — Loma Linda University
Contact: James J. Couperus, MD, Associate Dean for Educational Affairs, Loma Linda University School of Medicine, Loma Linda 92350.

PMC — Pacific Medical Center
Contact: Continuing Education, Pacific Medical Center, PO Box 7999, San Francisco 94120. (415) 563-4321, ext 2761.

STAN — Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Medical School Office Building, Suite X-365, Stanford 94305-6114. (415) 723-5594.

UCD — University of California, Davis
Contact: Ruth Feryok, Director, Office of Continuing Medical Education, University of California, Davis, School of Medicine, 2701 Stockton Blvd, Sacramento 95817. (916) 734-5390.

UCI — University of California, Irvine
Contact: Melvin I. Marks, MD, Director, Memorial/UCI Center for Health Education, Long Beach Memorial Medical Center, 2801 Atlantic Ave, PO Box 1428, Long Beach, California 90801-1428. (213) 595-3811.

UCLA — University of California, Los Angeles Extension
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, PO Box 24902, UCLA, Los Angeles 90024. (213) 825-8423.

UCSD — University of California, San Diego
Contact: Office of Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (619) 534-3940.

UCSF — University of California, San Francisco
Contact: Janet Johnson, Administrative Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 476-4251.

USC — University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 1975 Zonal Ave, KAM314, Los Angeles 90033. (213) 224-7051.

February 9-15—**UCI Family Practice Refresher Course.** Memorial/UCI Center for Health Education at Marriott Hotel, Newport Beach. Sun-Sat. Contact: UCI.

February 13-15—**Current Concepts in Cancer Management: A Symposium for Primary Care Physicians and Cancer Care Providers.** Hoag Memorial Center at Newport Beach Marriott. Thurs-Sat. $350. Contact: Meeting Management, 5665 Oberlin, Ste 110, San Diego 92121. (619) 453-6222.

February 13-16—**44th Annual Scientific Assembly.** California Academy of Family Physicians at Sheraton Harbor Island Hotel, San Diego. Thurs-Sun. 26 hrs. $275. Contact: Robert Fagan, CAFP, 114 Sansome St, Ste 1305, San Francisco 94104. (415) 394-9121.

February 14-16—**Office Gynecology for the Primary Care Physician.** SDSU at Hyatt Islandia, San Diego. Fri-Sun. 20 hrs. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

February 17-19—**Issues in Men's Health.** SDSU at Hyatt Islandia, San Diego. Mon-Wed. 20 hrs. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

March 25-27—**Annual Review in Family Medicine: Controversies and Challenges in Primary Care.** UCSF. Wed-Fri. 15.5 hrs. Contact: UCSF.

April 4-11—**5th Annual Primary Care Medicine: Update 1992.** UCSF at Maui Intercontinental, Wailea, Maui, Hawaii. 1 week. $540. Contact: UCSF.

April 9-11—**Advances in Rheumatology for Primary Care Physicians.** UCSF at Le Meridien Hotel, San Francisco. Thurs-Sat. $240. Contact: UCSF.

April 10—**Office Orthopedics for the Primary Care Physician.** Sharp Memorial Hospital at San Diego Princess Vacation Village, San Diego. Fri. 20 hrs. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

GASTROENTEROLOGY

February 29-March 1—**Endoscopy Update 1992.** Southern California Society for Gastroenterology at Century Plaza Hotel, Los Angeles. Sat-Sun. Contact: Joyce Fried, University of California Brain Research Institute, Los Angeles 90024.

GERIATRICS

January 21-25—**9th UCLA Intensive Course in Geriatric Medicine.** UCLA at Beverly Hilton. Tues-Sat. 40 hrs. $600. Contact: UCLA.

January 24-25—**Alzheimer's Disease: New Approaches to Treatment.** UCSD at Westgate Hotel, San Diego. Contact: Cass Jones, Professional Conference Management, 7916 Convoy Ct, San Diego 92111. (619) 565-9921.

March 6-8—**Recent Advances in Geriatric Medicine-Healthy People 2000: A New Look at Screening, Prevention and Rehabilitation in the Elderly.** UCSD at Pan Pacific Hotel, San Diego. Fri-Sun. Contact: Cass Jones, Professional Conference Management, 7916 Convoy Ct, San Diego 92111. (619) 565-9921.

INFECTIOUS DISEASES

February 7-8—**10th Annual Infectious Disease.** UCD. Fri-Sat. Contact: UCD.

April 29-May 1—**13th Annual Advances in Infectious Diseases.** UCSF at San Francisco. Wed-Fri. $400. Contact: UCSF.

INTERNAL MEDICINE

December 5—**Common Musculoskeletal Problems—Knee.** VA Medical Center Sepulveda. Thurs. 5.5 hrs. Contact: Arun Mehta, MD, VA Med Ctr, (818) 895-9344.

December 6-7—**Clinical Applications of New Advances in Internal Medicine.** UCD at Cancer Center Auditorium. Fri-Sat. 12 hrs. Contact: UCD.

January 30-February 1—**Advanced Nephrology: Nephrology for the Consultant.** UCSD at La Jolla Marriott, San Diego. Thurs-Sat. 17 hrs. $350. Contact: UCSD.

February 22-28—**Topics and Advances in Internal Medicine.** UCSD at Sheraton Harbor Island, San Diego. Sat-Sun. Contact: UCSD.

February 27-29—**1992 Zimmerman Conference: Progress in Vascular Biology, Hemostasis and Thrombosis.** Scripps Clinic at Sheraton Grande Torrey Pines Hotel, La Jolla. Thurs-Sat. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

(Continued on Page 468)

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- Childrens Hospital Los Angeles
- Doheny Eye Institute
- Kenneth Norris Jr. Cancer Hospital & Research Institute
- USC University Hospital

(Continued from Page 466)

March 20-26—**Internal Medicine 1992: A Comprehensive Review.** Sharp Memorial Hospital at Hotel del Coronado. Fri-Thurs. 54 hours. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

NEUROLOGY

January 1-February 1—**15th Annual: Neurology for Non-Neurologists.** UCSD at Omni San Diego Hotel. Thurs-Sat. 21 hrs. $425. Contact: UCSD.

February 13-15—**25th Annual Recent Advances in Neurology.** UCSF at San Francisco. Thurs-Sat. 15 hrs. Contact: UCSF.

OB/GYN

November 18-23—**14th Annual Review Course in Clinical OB/GYN and Gynecological Histopathology.** Memorial/UCI Center for Health Education at Westin South Coast Plaza, Costa Mesa. Mon-Sat. 44 hrs. Contact: UCI.

January 16-19—**OB/GYN and Ultrasound.** UCSD at Hotel del Coronado, San Diego. Thurs-Sun. 20 hrs. $450. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

February 2-6—**Ambulatory Gynecology.** UCD at Hyatt Lake Tahoe, Incline Village, Nevada. Sun-Thurs. Contact: UCD.

February 13-16—**47th Annual Postgraduate Assembly.** OB/GYN Assembly of Southern California at Beverly Hilton, Beverly Hills. Thurs-Sun. 28 hrs. Contact: OB/GYN Assembly, 5820 Wilshire Blvd, #500, Los Angeles 90036. (213) 937-5514.

April 2-4—**Gynecologic Surgery.** Memorial/UCI Center for Health Education at Marquis Hotel, Palm Springs. Thurs-Sat. Contact: UCI.

April 2-4—**Ultrasound Update.** Memorial/UCI Center for Health Education at Bally's Hotel, Las Vegas. Thurs-Sat. Contact: UCI.

April 8-12—**Pacific Coast Fertility Society: Annual Scientific Program and Postgraduate Course.** Pacific Coast Fertility Society at Stouffer Esmeralda Resort, Indian Wells. Wed-Sun. 22 hrs. Contact: Director of Medical Education, 12760 La Mirada Blvd, Ste 220, La Mirada 90638. (213) 947-7068.

OCCUPATIONAL/ENVIRONMENTAL

January 27-February 7—**Occupational and Environmental Medicine Series: Session I.** UCSF at Miyako Hotel, San Francisco. Mon-Fri. 80 hrs. $1200. Contact: UCSF.

February 10-14—**Occupational and Environmental Medicine: Session III.** UCSF at Miyako Hotel Japan Center, San Francisco. Mon-Fri. 40 hrs. $600. Contact: UCSF.

February 12-16—**Team Physician Course.** American College of Sports Medicine at Wyndham Hotel, Palm Springs. Wed-Sun. Contact: ACMS, PO Box 1440, Indianapolis, IN 46202-1440. (317) 637-9200.

ONCOLOGY

November 21-23—**3rd Annual Symposium on Diagnosis and Treatment of Musculoskeletal Tumors.** UCD at Hyatt Regency, Sacramento. Thurs-Sat. 16 hrs. $450. Contact: UCD.

December 11—**27th Annual Northern California Cancer Conference.** Enloe and Chico Community Hospital at Esplanade Building Enloe Hospital. Wed. Contact: Linda Spring, (916) 891-7375.

February 17-19—**Clinical Hematology and Oncology: 1992.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Mon-Wed. 18 hrs. $385. Contact: Susan Buntjer, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

March 5-7—**7th International Conference on Monoclonal Antibody Immunoconjugates for Cancer.** UCSD at San Diego Marriott. Thurs-Sat. Contact: UCSD.

April 30-May 3—**Breast Cancer Conference.** Memorial/UCI Center for Health Education at Hyatt Regency, Long Beach. Thurs-Sun. Contact: UCI.

OPHTHALMOLOGY

January 31-February 4—**11th Annual Squaw Valley Retina Symposium.** Alta-California Ophthalmological Society at Resort at Squaw Creek, Olympic Valley. Fri-Tues. 16 hrs. Contact: Richard Murray, 2701 Eye St, Sacramento 95816. (916) 442-4975.

ORTHOPEDICS

January 23-25—**Orthopaedic Update II: Current Concepts and Advances.** UCSD at Hyatt Islandia Hotel, San Diego. Thurs-Sat. Contact: UCSD.

January 23-26—**Fracture Management.** UCD at Resort at Squaw Creek, Squaw Valley. Thurs-Sun. Contact: UCD.

March 15-20—**The Spine: Current Concepts of Diagnosis and Treatment.** Vanderbilt University Medical Center Department of Orthopaedics at Grand Hyatt Wailea, Maui, Hawaii. Sun-Fri. $575. Contact: The Spine/Current Concepts, c/o Unconventional Inc, 3960 Park Blvd, Ste E, San Diego 92103. (619) 692-9115.

PAIN MANAGEMENT

November 15-16—**Pain Management.** UCD at Sterling Hotel, Napa. Fri-Sat. Contact: UCD.

December 11-15—**American Back Society Fall Symposium on Back Pain.** St. Francis Memorial Hospital Spine Center at Marriott, San Francisco. Wed-Sun. Contact: Aubrey Swartz, 2647 E 14th St, #401, Oakland 94601. (415) 536-9929.

February 19-22—**The Practicing Physician's Approach to the Difficult Headache Patient.** University of Chicago School of Medicine at Wyndham Hotel, Palm Springs. Wed-Sat. 15 hrs. Contact: Idell Applebaum, Diamond Headache Clinic, 5252 N Western Ave, Chicago, IL 60625. (312) 878-0396.

PATHOLOGY

January 10-11—**Pathology Update.** UCD at Cancer Center Auditorium. Fri-Sat. Contact: UCD.

April 11—**7th Annual Conference: New Treatment in Chronic Liver Disease.** Scripps Clinic and Research Foundation at La Jolla. Sat. 6 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

PEDIATRICS

November 20-23—**Pediatric Infectious Disease Seminar.** University of Toronto at Four Seasons Hotel, Newport Beach. Wed-Sat. Contact: University of Toronto, Medical Science Bldg, Toronto, Ontario M5S 1A8. (416) 978-2718.

January 22-25—**San Diego Conference on Responding to Child Maltreatment.** Children's Hospital at Hyatt Regency Hotel, La Jolla. Wed-Sat. Contact: Children's Hospital, 8001 Frost St, San Diego 92123. (619) 495-4940.

February 7-9—**Current Concepts in Pediatric Medicine: 1992.** Children's Hospital San Diego at Hyatt Islandia Hotel, San Diego. Fri-Sun. 18 hrs. Children's Hospital, (619) 576-4072.

March 4-6—**17th Annual Care of the Sick Newborn.** Memorial/UCI Center for Health Education at Long Beach. Wed-Fri. Contact: UCI.

PSYCHIATRY

January 26-31—**18th Annual Midwinter Program for Psychiatrists.** UCD at Hyatt Lake Tahoe. Sun-Fri. 25 hrs. $395. Contact: UCD.

February 1-3—**West Coast Neuropsychological Assessment Conference: Recent Advances in the Boston Approach to Neuropsychological Assessment.** UCSD at Pan Pacific Hotel, San Diego. Sun-Mon. Contact: Cass Jones, Professional Conference Management, 7916 Convoy Ct, San Diego 92111. (619) 565-9921.

February 8-9—**Breakthroughs in Anxiety Disorders: Treating Anxiety, Panic and Obsessive-Compulsive Disorders and Depression.** UCSD at Omni Hotel, San Diego. Sat-Sun. Contact: Cass Jones, Professional Conference Management, 7916 Convoy Ct, San Diego 92111. (619) 565-9921.

February 15-16—**Victims of Abuse: The Emotional Impact of Child and Adult Trauma.** San Diego Psychoanalytic Society and Institute at Hyatt Regency La Jolla at Aventine. Sat-Sun. Contact: Cass Jones, Professional Conference Management, 7916 Convoy Ct, San Diego 92111. (619) 565-9921.

March 13-15—**West Coast Psychiatry Board Review: Preparation for Part II.** UCSD at US Grant Hotel, San Diego. Fri-Sun. Contact: Cass Jones, Professional Conference Management, 7916 Convoy Ct, San Diego 92111. (619) 565-9921.

(Continued on Page 470)

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(Continued from Page 468)

April 10-11—**The Cutting Edge 1992: Erotic Mysteries—Intimacy, Sexuality and Gender in the '90s.** UCSD at Omni Hotel, San Diego. Fri-Sat. Contact: Cass Jones, Professional Conference Management, 7916 Convoy Ct, San Diego 92111. (619) 565-9921.

RADIOLOGY

November 15-17—**Advanced Seminars in Diagnostic Imaging.** UCSD at Ritz-Carlton Hotel, Laguna Niguel. Fri-Sun. $400. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

January 10-12—**Advanced Seminars in Diagnostic Imaging.** UCSD at Ritz-Carlton Resort Hotel, Laguna Niguel. Fri-Sun. 15 hrs. $400. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925 (404) 641-9773.

January 12-16—**Diagnostic Imaging Update: Body Imaging, Mammography, Neuroradiology and Pediatrics.** Stanford University Medical Center at Ritz-Carlton Palm Beach. Sun-Thurs. 23.5 hrs. $550. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

January 31-February 2—**44th Annual Midwinter Radiological Conference.** Los Angeles Radiological Society at Century Plaza Hotel, Los Angeles. Fri-Sun. 17.25 hrs. $425. Contact: LARS, PO Box 91215, Los Angeles 90009-1215. (213) 827-9078.

February 4-7—**Advanced Seminars in Diagnostic Imaging.** UCSD at Le Meridien Hotel, Coronado. Tues-Fri. 20 hrs. $500. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

February 4-8—**18th Annual Mid-Pacific Radiological Conference.** Los Angeles Radiological Society at Hyatt Regency Waikoloa, Hawaii. Tues-Sat. 18.5 hrs. $550. Contact: LARS, PO Box 91215, Los Angeles 90009-1215. (213) 827-9078.

February 10-13—**Mammographically Detected Early Breast Cancer.** University of Alabama at Birmingham at Ritz-Carlton, Rancho Mirage. Mon-Thurs. 18 hrs. $450. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

February 24-28—**Diagnostic Imaging Update: Body Imaging, Mammography, MRI and Interventional.** Stanford University Medical Center at Ritz-Carlton Mauna Lani, Hawaii. Mon-Fri. 23.5 hrs. $550. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

February 27-March 1—**Advanced Seminars in Diagnostic Imaging.** UCSD at Ritz-Carlton, Laguna Niguel. Thurs-Sun. 20 hrs. $500. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

March 2-6—**Magnetic Resonance Imaging.** UCSD at Hotel del Coronado, San Diego. Mon-Fri. 27.25 hrs. $540. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

March 22-27—**MRI Workshop in Hawaii: 1992.** Queens Medical Center at Kea Lani Hotel, Wailea, Hawaii. Sun-Fri. 37 hrs. $595. Contact: Susan Block, Queens Medical Ctr, 1301 Punchbowl St, Honolulu, HI 96813. (808) 547-4544.

April 19-24—**Residents Radiology Review Course.** UCSD at Hotel del Coronado, San Diego. Sun-Fri. 39 hrs. $470. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

April 25—**Interventional Radiology.** UCSD at Hotel del Coronado, San Diego. Sat. 8 hrs. $125. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

REHABILITATIVE/THERAPEUTIC

November 14-16—**3rd Triennial Symposium on New Directions in Antiviral Chemotherapy.** UCSF at Sheraton Palace Hotel, San Francisco. Thurs-Sat. 19 hrs. $200. Contact: UCSF.

March 5-7—**Rehabilitation: Science, Technology, Quality and Costs—Present and Future.** Scripps Memorial Hospital at La Jolla Marriott. 18.5 hrs. $395. Contact: Meeting Management, 5665 Oberlin Dr, Ste 110, San Diego 92121. (619) 453-6222.

SLEEP MEDICINE

January 30-31—**New Horizons in Sleep Disorders Medicine.** California Thoracic Society at Doubletree Resort, Palm Springs. Thurs-Fri. Contact: California Thoracic Society, 202 Fashion Ln, #219, Tustin 92680. (714) 730-1944.

April 3-4—**Pharmacotherapeutics in Clinical Sleep Medicine.** Scripps Clinic and Research Foundation at La Jolla. Fri-Sat. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

SURGERY

December 5-6—**Advanced Techniques in Laparoscopic Surgery.** UCD. Thurs-Fri. 15 hrs. $3200. Contact: UCD

January 17-18—**What's New in General Surgery.** UCD at Radisson Hotel, Sacramento. Fri-Sat. 16 hrs. $295. Contact: UCD.

February 8-11—**International Symposium on Hair Replacement Surgery.** American Academy of Facial Plastic and Reconstructive Surgery at Century City J W Marriott, Los Angeles. Sat-Tues. Contact: Sharon Clawson, (213) 278-8823.

February 9-14—**15th Annual San Diego Postgraduate Assembly in Surgery.** UCSD at Hotel del Coronado, San Diego. Sun-Fri. Contact: UCSD.

February 12-14—**2nd International Lung Transplant Symposium: Update 1992.** Cedars-Sinai Medical Center at Ritz-Carlton, Laguna Niguel. Wed-Fri. 6.5 hrs. $500. Contact: Carolyn Lavitt, Continuing Education, 8700 Beverly Blvd, Los Angeles 90048. (213) 855-5547.

March 19-22—**42nd Annual Surgical Forum.** Society of Graduate Surgeons at Beverly Hilton, Beverly Hills. Thurs-Sun. Contact: SGS, 5820 Wilshire Blvd, Ste 500, Los Angeles 90036. (213) 937-5514.

GENERAL/MULTIDISCIPLINARY

December 9-10—**Clinical Care of the AIDS Patient.** UCSF at San Francisco Marriott Hotel. Mon-Tues. 13 hrs. $250. Contact: UCSF.

January 25-27 and March 1-2—**Lactation Educator Training Programs.** UCLA at Loma Linda. 22.5 hrs. $725. Contact: UCLA.

February 24-28—**Physician Heal Thyself.** UCSD at San Diego Princess Resort. Mon-Fri. Contact: UCSD.

March 12-13—**Dimensions of Caring 1992: Enhancing Quality of Life in Palliative Care.** Scripps Clinic and Research Foundation at Omni Hotel, San Diego. Thurs-Fri. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

April 9-13—**Lactation Educator Training Programs.** UCLA at Westwood. 22.5 hrs. $725. Contact: UCLA.

COLORADO

This listing of continuing medical education programs in Colorado is compiled by the Denver Medical Society. To list CME programs here, please send information at least two months in advance to: Mr Robert L. Kennedy, Denver Medical Society, 1850 Williams Street, Denver, CO 80218; or telephone (303) 377-1850.

Brochures, course information, and registration forms are available from the contact person or organization.

November 22-23—**Colorado Springs Perinatal Conference.** Children's Hospital of Denver at Embassy Suites Hotel, Colorado Springs. Fri-Sat. Contact: Christine Sievers-Spencer, (303) 861-6413.

November 22-23—**Cleft Lip and Palate Symposium.** Children's Hospital, Denver. Fri-Sat. Contact: Christine Sievers-Spencer, (303) 861-6413.

December 2-6—**Respiratory Therapy Traineeship Program.** Children's Hospital, Denver. Mon-Fri. Contact: Jeff Griebel, (303) 861-6188.

December 6-8—**Primary Care Office Computing.** University of Colorado School of Medicine at The Broker Inn, Boulder. Fri-Sun. Contact: Joann Bauer, (303) 270-5241.

December 6-8—**Advanced Laparoscopy for the General Surgeon.** Rose Medical Center and University of Colorado School of Medicine at Loew's Giorgio Hotel and University of Colorado Health Sciences Center, Denver. Fri-Sat. Contact: David R. Scott, (800) 525-5810.

December 21-April 11, 1992 (17 Weekly Meetings)—**Second Annual Vail Computers in Medicine Conference.** Rose Medical Center at L' Ostello Lodge, Vail. One week. Contact: David R. Scott, (800) 525-5810.

January 9-11—**Twenty-Seventh Annual Conference on Occupational Medicine & Colorado/AMA Guides to Evaluation of Permanent Impairment Course.** The Rocky Mountain Academy of Occupational Medicine and Colorado State Association of Occupational Health Nurses at Hyatt Regency Tech Center, Denver. Thurs-Sat. Contact: Douglas Scott, MD, (303) 782-9129.

January 25-February 1—**Reconstructive Surgery of the Hip and Knee.** University of Colorado School of Medicine at Snowmass Conference Center, Snowmass Village. One week. Contact: Joann Bauer, (303) 270-5195 or (800) 882-9153.

January 25-February 1—**15th Annual Infectious Diseases in Clinical Practice.** UCSF at Beaver Run Resort and Conference Center, Breckenridge. Sat-Sat. 24 hrs. Contact: UCSF.

(Continued on Page 472)

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References:

1. A. Morales et al., New England Journal of Medicine: 1221. November 12, 1981
2. Goodman, Gilman — The Pharmacological basis of Therapeutics 6th ed., p. 176-188. McMillan December Rev 1/85.
3. Weekly Urological Clinical Letter, 27:2, July 4, 1983.
4. A. Morales et al., The Journal of Urology 128. 45-47, 1982.

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CONTINUING MEDICAL EDUCATION

(Continued from Page 470)

February 8-15—**Seventeenth Annual Vail Psychiatry Conference.** Rose Medical Center and University of Colorado School of Medicine at Lion Square Lodge, Vail. One week. Contact: David R. Scott, (800) 525-5810.

February 8-15—**Sixth Annual Duke Symposium on Dermatologic and Rheumatic Diseases.** Duke University Medical Center at Marriott Mark Resort, Vail. One week. Contact: Symposium Coordinator, Duke University, (800) 457-1125.

February 8-15—**Fourteenth Annual Vail Emergency Medicine Conference.** Rose Medical Center and University of Colorado School of Medicine at Marriott Mark Resort, Vail. One week. Contact: David R. Scott, (800) 525-5810.

February 10-14—**Family Practice Review,** University of Colorado School of Medicine, Denver. Mon-Fri. Contact: Joann Bauer, (303) 270-5195 or (800) 882-9153.

February 14-16—**Advanced Laparoscopy for the General Surgeon.** Rose Medical Center and University of Colorado School of Medicine at Loew's Giorgio Hotel and University of Colorado Health Sciences Center, Denver. Fri-Sun. Contact: David R. Scott, (800) 525-5810.

February 15-22—**Eighteenth Annual Vail Obstetrics and Gynecology Conference.** Rose Medical Center and University of Colorado School of Medicine at Marriott Mark Resort, Vail. One week. Contact: David R. Scott, (800) 525-5810.

February 15-22—**Seventeenth Annual Vail Internal Medicine Conference.** Rose Medical Center and University of Colorado School of Medicine at Lion Square Lodge, Vail. One week. Contact: David R. Scott, (800) 525-5810.

February 28-March 2—**Principles of Anesthesia Technology.** University of Colorado School of Medicine at Marriott Mark Resort, Vail. Fri-Mon. Contact: Joann Bauer, (303) 270-5195 or (800) 882-9153.

February 22-29—**Seventeenth Annual Vail General and Vascular Surgery Conference.** Rose Medical Center and University of Colorado School of Medicine at Marriott Mark Resort, Vail. One week. Contact: David R. Scott, (800) 525-5810.

February 22-29—**Neurology for the Primary Care Physician.** Rose Medical Center and University of Colorado School of Medicine at The Antlers at Vail. One week. Contact: David R. Scott, (800) 525-5810.

February 29-March 7—**Colorado Review of Anesthesia.** University of Colorado School of Medicine at Marriott Mark Resort, Vail. One week. Contact: Joann Bauer, (303) 270-5195 or (800) 882-9153.

February 29-March 7—**Horizons in Surgery.** University of Colorado School of Medicine at Beaver Run Resort, Breckenridge. One week. Contact: Joann Bauer, (303) 270-5195 or (800) 882-9153.

February 29-March 7—**Third Annual Vail Infectious Disease Conference.** Rose Medical Center and University of Colorado School of Medicine at The Antlers at Vail. One week. Contact: David R. Scott, (800) 525-5810.

February 29-March 7—**Fourteenth Annual Vail Pediatrics Conference.** Rose Medical Center and University of Colorado School of Medicine at Marriott Mark Resort, Vail. One week. Contact: David R. Scott, (800) 525-5810.

March 7-14—**Seventeenth Annual Vail Primary Care Conference.** Rose Medical Center and University of Colorado School of Medicine at Marriott Mark Resort, Vail. One week. Contact: David R. Scott, (800) 525-5810.

March 7-14—**"Minding the Body, Mending the Mind": Influencing Health and Healing.** Rose Medical Center and University of Colorado School of Medicine at The Antlers at Vail. One week. Contact: David R. Scott, (800) 525-5810.

March 7-14—**Fifteenth Annual Vail Cancer Treatment Conference.** Rose Medical Center and University of Colorado School of Medicine at The Antlers at Vail. One week. Contact: David R. Scott, (800) 525-5810.

March 14-21—**Fifteenth Annual Vail Urology Conference.** Rose Medical Center and University of Colorado School of Medicine at Marriott Mark Resort, Vail. One week. Contact: David R. Scott, (800) 525-5810.

March 14-21—**Fourteenth Annual Vail Sports Medicine Conference.** Rose Medical Center and University of Colorado School of Medicine at Marriott Mark Resort, Vail. One week. Contact: David R. Scott, (800) 525-5810.

March 16-19—**Nineteenth Annual Neonatal and Infant Respiratory Symposium.** Ohio State University Hospitals at Marriott Mark Resort, Vail. Mon-Thurs. Contact: Arlene Rogers, Ohio University Hospitals, (614) 293-8487.

March 21-28—**Headache and Facial Pain Conference.** Rose Medical Center and University of Colorado School of Medicine at The Antlers at Vail. One week. Contact: David R. Scott, (800) 525-5810.

March 21-28—**Fourth Annual Colorado Geriatrics Overview/Board Review.** University of Colorado School of Medicine at Iron Horse Resort, Winter Park. One week. Contact: Joann Bauer, (303) 270-5195 or (800) 882-9153.

(Continued on Page 473)

(Continued from Page 472)

First Wednesday of Each Month—**Various Topics in Neurology.** Sponsored by the Colorado Society of Clinical Neurologists. Contact: Colorado Society of Neurologists, (303) 449-3566.

CONTACT INFORMATION

U of Colo—Contact: University of Colorado School of Medicine, Office of Continuing Medical Education, 4200 E 9th Ave, Denver, CO (303) 270-5195

IDAHO

February 21-23—**33rd Annual Medical Winter Clinics—Wilderness and Travel Medicine.** Ada County Medical Society at Shore Lodge, McCall. Fri-Sun. 9 hrs. Cat. 1. $100 for Idaho Medical Association members; $150, nonmembers. Contact: Judy Barningham, Ada County Medical Society, PO Box 2668, Boise 83701. (208) 336-2930.

NEW MEXICO

Information, requests for accreditation, and items to be listed should be sent to the chair of the CME Committee, New Mexico Medical Society, 7770 Jefferson, Suite 400, Albuquerque, NM 87109, at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 828-0237.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

November 15-16—**The Diagnosis and Management of Anxiety Disorders.** Marriott Hotel, Albuquerque. Contact: Lee Stephenson, University of New Mexico School of Medicine, Office of CME, PO Box 713, Albuquerque 87131, (505) 277-3942.

November 22-23—**Trauma Update '91.** Holiday Inn Pyramid, Albuquerque. Contact: University of New Mexico School of Medicine, Office of CME, PO Box 713, Albuquerque 87131. (505) 277-3942.

December 5-7—**American College of Physicians Annual Scientific Meeting.** Marriott Hotel, Albuquerque. Contact: Linda Alsup, University of New Mexico School of Medicine, Office of CME, PO Box 713, Albuquerque 87131, (505) 277-3942; or Elsa Hall, New Mexico Medical Society, (505) 828-0237.

February 28-29—**20th Annual New Mexico Thoracic Society Lung Disease Conference.** El Dorado Hotel, Santa Fe. Contact: Billie Dytzel, 216 Truman, NE, Albuquerque 87108. (505) 265-0732.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. Accredited institutions wishing to list AMA Category 1 CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, UT 84102; or phone (801) 355-5290. For information on CME accreditation, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution.

MEDICAL GRAND ROUNDS

Each Wed—8:00-9:00 a.m. Alternating between University of Utah Medical Center and VA Medical Center, Salt Lake City. Contact: William D Odell, MD, PhD, Professor and Chairman, Dept of Internal Medicine, Univ of Utah, (801) 581-7606.

* * *

November 15-16—**Laser Surgery—Laparoscopic Cholesystectomy** (Sponsor: UUSM). Fri-Sat. The Laser Institute, University of Utah, Salt Lake City. Contact: (801) 581-7001.

February 14-15—**1992 Winter Ski Meeting** (Sponsor: Utah Ophthalmological Society). Fri-Sat. Prospector Square Hotel, Park City. Contact: Mark Fotheringham, (801) 355-7477.

SPONSORS OF COURSES—ABBREVIATIONS

AHA	American Heart Association, Utah Affiliate, 645 E 400 South, Salt Lake City 84102. (801) 322-5601.
CH:	Castleview Hospital (formerly Carbon Hospital), RFD 2, Box 46, Price 84501. (801) 637-4800
HCH:	Holy Cross Hospital, 1045 E First South, Salt Lake City 84102. (801) 350-4744
ITS	Intermountain Thoracic Society, 1616 S 11th East, Salt Lake City 84105. (801) 484-4456.
LDSH	LDS Hospital, 8th Ave and "C" St, Salt Lake City 84143. (801) 321-1100.
LRH	Logan Regional Hospital, 1400 N 5th East, Logan 84321. (801) 752-2050.
MDH	McKay-Dee Hospital Center, 3939 Harrison Blvd, Ogden 84409. (801) 399-4141.
MVH	Mountain View Hospital, 1000 E Highway 6, Payson 84651. (801) 465-9201.
144	144th Evacuation Hospital, PO Box 8000, Salt Lake City 84108. (801) 524-3924
OSS	Ogden Surgical Society, PO Box 9311, Ogden 84409.
PVH:	Pioneer Valley Hospital, 3460 S 4155 West, West Valley City 84120. (801) 968-9061.
UOS	Utah Ophthalmological Society, 540 E 500 South, Salt Lake City 84102. (801) 355-7477.
USH:	Utah State Hospital, PO Box 270, Provo 84603-0270. (801) 373-4400.
UUSM:	University of Utah School of Medicine, Office of Continuing Medical Education, 50 N Medical Dr, Salt Lake City 84132. (801) 581-8664.
VAMC:	Veterans Administration Medical Center, 500 Foothill Dr, Salt Lake City 84148 (801) 582-1565.
VVMC:	Valley View Medical Center, 595 S 75 East, Cedar City 84720. (801) 586-6587.
WRI:	Western Rehabilitation Institute, 8074 S 1300 East, Sandy 84094. (801) 561-3400.

WASHINGTON

The listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here, please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle, WA 98121; or phone (206) 441-WSMA.

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

November 14-15—**Drug Therapy.** Seattle. Thurs-Fri. Contact: U/W.

November 15—**25th Annual Cancer Conference: Screening and Symptom Management for the Primary Care Provider.** Seattle. Fri. Contact: VMMC.

November 22—**Cardiology Conference.** Seattle. Fri. Contact: Swedish Hospital, (206) 386-2265.

November 22-23—**Advanced Pediatric Life Support.** Seattle. Fri-Sat. Contact: ACEP, (206) 441-9762.

December 6—**Practical Pediatrics.** Seattle. Fri. Contact: VMMC.

December 6-7—**Urology.** Seattle. Fri-Sat. Contact: (206) 441-9762.

December 12-13—**Advanced Cardiac Life Support.** Tacoma. Thurs-Fri. Contact: PCMS.

December 12-14—**American College of Physicians.** Seattle. Thurs-Sat. Contact: U/W.

December 12-14—**7th Annual ID Conference.** Everett. Thurs-Sat. Contact: Pacific Northwest Medical Education Institute, (206) 258-6322.

(Continued on Page 474)

CONTINUING MEDICAL EDUCATION

(Continued from Page 473)

January 16—**Law and Medicine Symposium.** Tacoma. Thurs. Contact: PCMS.

January 16-17—**Alzheimers Update.** Seattle. Thurs-Fri. Contact: U/W.

January 24-25—**WTS Chest Conference.** Seattle. Fri-Sat. Contact: Washington Thoracic Society, (206) 441-5100.

January 31—**Vascular Surgery Update for Primary Care Providers.** Seattle. Fri. Contact: VMMC.

February 6-7—**A Day in the Office: Problems in Pediatric Practice 1992.** Seattle. Thurs-Fri. Contact: Group Health, (206) 326-3441.

February 7—**Review of HIV Infections.** Tacoma. Fri. Contact: PCMS.

February 14—**Cancer and the Nervous System.** Seattle. Fri. Contact: VMMC.

February 28—**Office Intervention: Alcohol and Substance Abuse.** Tacoma. Fri. Contact: PCMS.

March 9-13—**Geriatric Board Review.** Seattle. Mon-Fri. Contact: U/W.

March 9-19—**Physical Medicine and Rehabilitation.** Bellevue. Mon-Thurs. Contact: U/W.

March 12-13—**Internal Medicine Review—1992.** Tacoma. Thurs-Fri. Contact: PCMS.

March 20—**Integrated Approach to the Dizzy Patient.** Seattle. Fri. Contact: VMMC.

March 22-25—**Urgent Problems in Primary Care.** Bend, Oregon. Sun-Thurs. Contact: Group Health, (206) 326-3441.

March 25—**Ethics Conference.** Seattle. Wed. Contact: VMMC.

March 23-26—**Death Investigations.** Seattle. Mon-Thurs. Contact: U/W.

March 25-27—**Spirometry Training for Worker Screening.** Seattle. Wed-Fri. Contact: NW Center for Occupational Health and Safety, (206) 543-1069.

March 30-April 3—**Hawaii and CME.** Kauai, Hawaii. Mon-Fri. Contact: PCMS.

April 10—**Recent Developments in Occupational Medicine.** Seattle. Fri. Contact: NW Center for Occupational Health and Safety, (206) 543-1069.

April 10—**Gastro-Esophageal Reflux: A Multi-faceted Disease.** Seattle. Fri. Contact: VMMC.

April 17-18—**Tacoma Surgical Club.** Tacoma. Fri-Sat. Contact: PCMS.

April 24—**Annual Day of Pediatrics.** Tacoma. Fri. Contact: Multicare, (206) 594-1221.

April 24-25—**Diabetes of the Eye.** Seattle. Fri-Sat. Contact: U/W.

April 24-25—**Low-Back Pain.** Seattle. Fri-Sat. Contact: VMMC.

April 30-May 2—**Musculoskeletal Disease.** Seattle. Thurs-Sat. Contact: U/W.

May 8—**Office Procedures.** Tacoma. Fri. Contact: PCMS.

May 13-15—**Fifth Conference on Occupational Hazards to Health Care Workers.** Seattle. Wed-Fri. Contact: NW Center for Occupational Health and Safety, (206) 543-1069.

May 21-22—**Cardiology Conference.** Tacoma. Thurs-Fri. Contact: Multicare, (206) 594-1221.

May 27—**Pesticide Medicine.** Eastern Washington. Wed. Contact: NW Center for Occupational Health and Safety, (206) 543-1069.

May 30—**The Fetal Patient.** Seattle. Sat. Contact: VMMC.

June 22-23—**Advanced Cardiac Life Support.** Tacoma. Mon-Tues. Contact: PCMS.

June 26—**Sports Medicine.** Tacoma. Fri. Contact: Multicare, (206) 594-1221.

September 9-12—**Washington State Medical Association Annual Meeting.** Jantzen Beach, Oregon. Thurs-Sun. Contact: WSMA.

September 23-24—**Critical Care.** Tacoma. Thurs-Fri. Contact: Multicare, (206) 594-1221. ◆

COURSE SPONSORS AND CONTACT INFORMATION

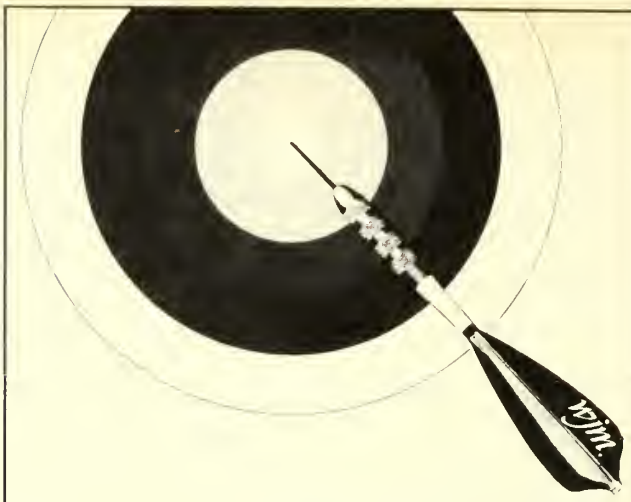
CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept of Pathology, Harborview Medical Center, 325 Ninth Avenue, Seattle, WA 98104. (206) 223-5953.

PCMS CME—Contact: Mrs Maxine Bailey, Executive Director, College of Medical Education, 705 South Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON)—Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

WSMA—Washington State Medical Association, Continuing Medical Education, 2033 Sixth Ave, Suite 900, Seattle, WA 98121. (206) 441-9762.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, PO Box 900, Seattle, WA 98111. (206) 223-6898.



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ABSTRACTS NOVEMBER 1991

(Szpakowski JL, Cox K, Nakazato P, Concepcion W, Levin B, Esquivel CO: Liver transplantation—Experience with 100 cases. West J Med 1991 Nov; 155:494-499)

Between March 1988 and November 1989, 100 liver transplants were performed on 90 patients at Pacific Presbyterian (now California Pacific) Medical Center in San Francisco. The immunosuppressive regimen was a combination of prophylactic Minnesota antilymphocyte globulin, cyclosporine, and low-dose corticosteroids. Rejections were treated with OKT3, a monoclonal antibody, or corticosteroids. Of the 100 transplants, 32 were done on 30 children, 18 of whom weighed less than 10 kg and 9 of whom received livers that had been surgically reduced in size to fit the recipient. The overall patient survival at 2 years was 85%. Of 100 liver transplants, treatment was given for 80 (80%) for at least 1 episode of rejection. At least 1 episode of serious infection occurred in 34 of the 60 adult patients and 25 of the 30 children. Of the entire group, 2% had hepatic artery thrombosis, and 12% had biliary complications that necessitated reoperation. The quality of life has been good, with a follow-up from 1 to almost 3 years (mean = 22 months). Comparing these data with those of other published series shows a decreased incidence of surgical complications and a lower rate of fungal and viral infections. We attribute this to the reduction of steroid dosage during convalescence without jeopardizing patient or graft survival.

LIVER TRANSPLANT IMMUNOSUPPRESSIVE THERAPY
ANTIREJECTION THERAPY

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LIVER TRANSPLANT IMMUNOSUPPRESSIVE THERAPY
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Bradford, R.H. et al.: Expanded clinical evaluation of lovastatin (EXCEL) study results: I. Efficacy in modifying plasma lipoproteins and adverse event profile in 8,245 patients with moderate hypercholesterolemia, *Archives of Internal Medicine,* January 1991.

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MEVACOR® (Lovastatin, MSD) is contraindicated in patients who are hypersensitive to any component of the medication; in patients with active liver disease or unexplained persistent transaminase elevations; in pregnant or lactating patients; and in women of childbearing age, except when such patients are highly unlikely to conceive.

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For many patients with primary hypercholesterolemia (Types IIa and IIb), when diet and other nondrug therapies are inadequate

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Atherosclerosis is a chronic process and the discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. Moreover, cholesterol and other products of the cholesterol biosynthesis pathway are essential components for fetal development, including synthesis of steroids and cell membranes. Because of the ability of inhibitors of HMG-CoA reductase such as MEVACOR® (Lovastatin, MSD) to decrease the synthesis of cholesterol and possibly other products of the cholesterol biosynthesis pathway, MEVACOR may cause fetal harm when administered to a pregnant woman. Therefore, lovastatin is contraindicated during pregnancy. Lovastatin should be administered to women of childbearing age only when such patients are highly unlikely to conceive. If the patient becomes pregnant while taking this drug, lovastatin should be discontinued and the patient should be apprised of the potential hazard to the fetus.

WARNINGS. *Liver Dysfunction*. **Marked persistent increases (to more than 3 times the upper limit of normal) in serum transaminases occurred in 1.9% of adult patients who received lovastatin for at least one year in clinical trials (see ADVERSE REACTIONS).** When the drug was interrupted or discontinued in these patients, the transaminase levels usually fell slowly to pretreatment levels. The increases usually appeared 3 to 12 months after the start of therapy with lovastatin and were not associated with jaundice or other clinical signs or symptoms. There was no evidence of hypersensitivity. A liver biopsy was done in one of these patients and showed areas of focal hepatitis. In this patient, transaminase levels returned to normal following discontinuation of therapy. Some of these patients had abnormal liver function tests prior to lovastatin therapy and or consumed substantial quantities of alcohol.

It is recommended that liver function tests be performed before treatment begins, every 4 to 6 weeks during the first 15 months of therapy with lovastatin, and periodically thereafter in all patients. Special attention should be paid to patients who develop elevated serum transaminase levels, and in these patients, measurements should be repeated promptly and then performed more frequently. If the transaminase levels show evidence of progression, particularly if they rise to 3 times the upper limit of normal and are persistent, the drug should be discontinued. Liver biopsy should be considered if elevations are persistent beyond the discontinuation of the drug.

The drug should be used with caution in patients who consume substantial quantities of alcohol and or have a past history of liver disease. Active liver disease or unexplained transaminase elevations are contraindications to the use of lovastatin.

As with other lipid-lowering agents, moderate (less than 3 times the upper limit of normal) elevations of serum transaminases have been reported following therapy with MEVACOR (see ADVERSE REACTIONS). These changes appeared soon after initiation of therapy with MEVACOR, were often transient, were not accompanied by any symptoms, and interruption of treatment was not required.

Skeletal Muscle. **Rhabdomyolysis has been associated with lovastatin therapy alone, when combined with immunosuppressive therapy including cyclosporine in cardiac transplant patients, and when combined in non-transplant patients with either gemfibrozil or lipid-lowering doses (≥1 g/day) of nicotinic acid. Some of the affected patients had preexisting renal insufficiency, usually as a consequence of long-standing diabetes. Acute renal failure from rhabdomyolysis has been seen more commonly with the lovastatin-gemfibrozil combination and has also been reported in transplant patients receiving lovastatin plus cyclosporine.**

Rhabdomyolysis with or without renal impairment has been reported in seriously ill patients receiving erythromycin concomitantly with lovastatin. Therefore, patients receiving concomitant lovastatin and erythromycin should be carefully monitored.

Fulminant rhabdomyolysis has been seen as early as 3 weeks after initiation of combined therapy with gemfibrozil and lovastatin but may be seen after several months. For these reasons, it is felt that, in most subjects who have had an unsatisfactory lipid response to either drug alone, the possible benefits of combined therapy with lovastatin and gemfibrozil do not outweigh the risks of severe myopathy, rhabdomyolysis, and acute renal failure. While it is not known whether this interaction occurs with fibrates other than gemfibrozil, myopathy and rhabdomyolysis have occasionally been associated with the use of other fibrates alone, including clofibrate. Therefore, the combined use of lovastatin with other fibrates should generally be avoided.

Physicians contemplating combined therapy with lovastatin and lipid-lowering doses of nicotinic acid or with immunosuppressive drugs should carefully weigh the potential benefits and risks and should carefully monitor patients for any signs and symptoms of muscle pain, tenderness, or weakness, particularly during the initial months of therapy and during any periods of upward dosage titration of either drug. Periodic CPK determinations may be considered in such situations, but there is no assurance that such monitoring will prevent the occurrence of severe myopathy. The monitoring of lovastatin drug and metabolite levels may be considered in transplant patients who are treated with immunosuppressives and lovastatin.

Lovastatin therapy should be temporarily withheld or discontinued in any patient with an acute, serious condition suggestive of a myopathy or having a risk factor predisposing to the development of renal failure secondary to rhabdomyolysis, including severe acute infection, hypotension, major surgery, trauma, severe metabolic, endocrine, and electrolyte disorders, and uncontrolled seizures.

Myalgia has been associated with lovastatin therapy. Transient, mildly elevated creatine phosphokinase levels are commonly seen in lovastatin-treated patients. However, in clinical trials, approximately 0.5% of patients developed a myopathy, i.e., myalgia or muscle weakness associated with markedly elevated CPK levels. Myopathy should be considered in any patient with diffuse myalgias, muscle tenderness, or weakness, and or marked elevation of CPK. Patients should be advised to report promptly unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever. Lovastatin therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected.

Most of the patients who have developed myopathy (including rhabdomyolysis) while taking lovastatin were receiving concomitant therapy with immunosuppressive drugs, gemfibrozil, or lipid-lowering doses of nicotinic acid. In clinical trials, about 30% of patients on concomitant immunosuppressive therapy including cyclosporine developed myopathy, the corresponding percentages for gemfibrozil and niacin were approximately 5% and 2%, respectively.

In 6 patients with cardiac transplants taking immunosuppressive therapy including cyclosporine concomitantly with lovastatin 20 mg/day, the average plasma level of active metabolites derived from lovastatin was elevated to approximately 4 times the expected levels. Because of an apparent relationship between increased plasma levels of active metabolites derived from lovastatin and myopathy, the daily dosage in patients taking immunosuppressants should not exceed 20 mg/day (see DOSAGE AND ADMINISTRATION). Even at this dosage, the benefits and risks of using lovastatin in patients taking immunosuppressants should be carefully considered.

PRECAUTIONS. *General*: Before instituting therapy with MEVACOR® (Lovastatin, MSD), an attempt should be made to control hypercholesterolemia with appropriate diet, exercise, weight reduction in obese patients, and to treat other underlying medical problems (see INDICATIONS AND USAGE).

Lovastatin may elevate creatine phosphokinase and transaminase levels (see ADVERSE REACTIONS). This should be considered in the differential diagnosis of chest pain in a patient on therapy with lovastatin.

Homozygous Familial Hypercholesterolemia. MEVACOR is less effective in patients with the rare homozygous familial hypercholesterolemia, possibly because these patients have no functional LDL receptors. MEVACOR appears to be more likely to raise serum transaminases (see ADVERSE REACTIONS) in these homozygous patients.

Drug Interactions. *Immunosuppressive Drugs, Gemfibrozil, Niacin (Nicotinic Acid), Erythromycin*: See WARNINGS, *Skeletal Muscle*.

Coumarin Anticoagulants: In a clinical trial in warfarin-treated patients designed specifically to observe a potential effect of lovastatin on the prothrombin time, lovastatin in dosages up to 40 mg b.i.d. did not produce any consistent alteration of the anticoagulant action of warfarin. However, since the drug was marketed, clinically evident bleeding and/or increased prothrombin time have been reported in a few patients taking coumarin anticoagulants concomitantly with lovastatin. The causal relationship to lovastatin is unclear. Nevertheless, it is recommended that in patients taking anticoagulants, prothrombin time be determined before starting lovastatin and frequently enough during early therapy to insure that no significant alteration of prothrombin time occurs. Once a stable prothrombin time has been documented, prothrombin times can be monitored at the intervals usually recommended for patients on coumarin anticoagulants. If the dose of lovastatin is changed, the same procedure should be repeated. Lovastatin therapy has not been associated with bleeding or with changes in prothrombin time in patients not taking anticoagulants.

Antipyrine: Antipyrine is a model for drugs metabolized by the microsomal hepatic enzyme system (cytochrome P450 system). Because lovastatin had no effect on the pharmacokinetics of antipyrine, interactions with other drugs metabolized via this mechanism are not expected.

Propranolol: In normal volunteers, there was no clinically significant pharmacokinetic or pharmacodynamic interaction with concomitant administration of single doses of lovastatin and propranolol.

Digoxin: In patients with hypercholesterolemia, concomitant administration of lovastatin and digoxin resulted in no effect on digoxin plasma concentrations.

Other Concomitant Therapy: Although specific interaction studies were not performed, in clinical studies, lovastatin was used concomitantly with beta blockers, calcium channel blockers, diuretics, and nonsteroidal anti-inflammatory drugs (NSAIDs) without evidence of clinically significant adverse interactions.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a 21-month carcinogenic study in mice, a statistically significant ($p < 0.05$) increase in the incidence of hepatocellular carcinomas and adenomas was observed at doses of 500 mg/kg/day (312 times the maximum recommended human dose) of lovastatin. These changes were not seen in mice given doses of 20 and 100 mg/kg/day (12.5 and 62.5 times the maximum recommended human dose).

A statistically significant increase ($p \leq 0.05$) in the incidence of pulmonary adenomas was seen in female mice receiving 500 mg/kg/day (312 times the maximum recommended human dose). No similar changes were seen in males at any dose or in females receiving 20 or 100 mg/kg/day (12.5 or 62.5 times the maximum recommended human dose). Because the incidence of pulmonary tumors was within the range of untreated animals in studies of similar duration, the relationship of this latter change to treatment is not known.

In addition, an increase in the incidence of papilloma in the non-glandular mucosa of the stomach was observed in mice receiving 100 and 500 mg/kg/day (62.5 and 312 times the maximum recommended human dose). No increase was seen at a dosage of 20 mg/kg/day (12.5 times the maximum recommended human dose). The glandular mucosa was not affected. The human stomach contains only glandular mucosa. Importantly, there is a strong association between this change and hyperplasia of the squamous epithelium (acanthosis) in this region, acanthosis is a characteristic change observed in the non-glandular mucosa of rodents treated with HMG-CoA reductase inhibitors and is most probably a result of inhibition of the reductase in this tissue.

Similar squamous epithelium is found in the esophagus and anorectal junction of the mouse and rat, however, no evidence of a similar drug-induced hyperplastic response was observed in these tissues in studies of up to 21 months in the mouse given up to 500 mg/kg/day (312 times the maximum recommended human dose), or in a study of 24 months in the rat given 180 mg/kg/day (112 times the maximum recommended human dose).

In a 24-month carcinogenicity study in rats, there was a positive dose response relationship for hepatocellular carcinogenicity in males (unadjusted $p = 0.025$). However, because the incidence of hepatocellular carcinogenicity observed in male rats in this study is similar to that observed spontaneously in this strain of rat, the implications of this finding are unclear.

Drug-related testicular atrophy, decreased spermatogenesis, spermatocytic degeneration and giant cell formation were seen in dogs starting at 20 mg/kg/day (12.5 times the maximum recommended human dose). The clinical significance of these findings is unclear.

No evidence of mutagenicity was observed in a microbial mutagen test using mutant strains of *Salmonella typhimurium* with or without rat or mouse liver metabolic activation. In addition, no evidence of damage to genetic material was noted in an *in vitro* alkaline elution assay using rat or mouse hepatocytes, a V-79 mammalian cell forward mutation study, an *in vitro* chromosome aberration study in CHO cells, or an *in vivo* chromosomal aberration assay in mouse bone marrow.

No drug-related effects on fertility were found in studies with rats.

Pregnancy: Pregnancy Category X. See CONTRAINDICATIONS.

Lovastatin has been shown to produce skeletal malformations in the rat fetus at doses of 800 mg/kg/day (500 times the maximum recommended human dose). At similar doses in mice, an increase in skeletal malformations was observed. These individual changes are within the range of those observed spontaneously in this strain of mouse. No drug-induced changes were seen in either species at doses of up to 80 mg/kg/day (50 times the maximum recommended human dose). No evidence of malformations was noted in rabbits at up to 15 mg/kg/day (highest tolerated dose – about 9 times the maximum recommended human dose). There are no data in pregnant women.

Nursing Mothers: Studies in rats have shown that lovastatin is excreted in the milk. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from MEVACOR, women taking lovastatin should not nurse their infants (see CONTRAINDICATIONS).

Pediatric Use: Safety and effectiveness in children have not been established. Because children are not likely to benefit from cholesterol lowering for at least a decade and because experience with this drug is limited (no studies in subjects below the age of 20 years), treatment of children with lovastatin is not recommended at this time.

ADVERSE REACTIONS. MEVACOR is generally well tolerated, adverse reactions usually have been mild and transient. Less than 1% of patients were discontinued from controlled clinical studies due to adverse experiences attributable to MEVACOR. About 2% of patients were discontinued from all studies (controlled and uncontrolled) due to adverse experiences attributable to MEVACOR, about one-third of these patients were discontinued due to increases in serum transaminases.

Clinical Adverse Experiences: Adverse experiences reported in patients treated with MEVACOR® (Lovastatin, MSD) in controlled clinical studies are shown in the table below.

	MEVACOR (N = 613) %	Placebo (N = 82) %	Cholestyramine (N = 88) %	Probucol (N = 97) %
Gastrointestinal				
Constipation	4.9	—	34.1	2.1
Diarrhea	5.5	4.9	8.0	10.3
Dyspepsia	3.9	—	13.6	3.1
Flatus	6.4	2.4	21.6	2.1
Abdominal pain/cramps	5.7	2.4	5.7	5.2
Heartburn	1.6	—	8.0	—
Nausea	4.7	3.7	9.1	6.2
Musculoskeletal				
Muscle cramps	1.1	—	1.1	—
Myalgia	2.4	1.2	—	—
Nervous System/Psychiatric				
Dizziness	2.0	1.2	—	1.0
Headache	9.3	4.9	4.5	8.2
Skin				
Rash/pruritus	5.2	—	4.5	—
Special Senses				
Blurred vision	1.5	—	1.1	3.1
Dysgeusia	0.8	—	1.1	—

Laboratory Tests: Marked persistent increases of serum transaminases have been noted (see WARNINGS).

About 11% of patients had elevations of creatine phosphokinase (CPK) levels of at least twice the normal value on one or more occasions. The corresponding values for the control agents were cholestyramine, 9% and probucol, 2%. This was attributable to the noncardiac fraction of CPK. Large increases in CPK have sometimes been reported (see WARNINGS, *Skeletal Muscle*).

Concomitant Therapy: In controlled clinical studies in which lovastatin was administered concomitantly with cholestyramine, no adverse reactions peculiar to this concomitant treatment were observed. The adverse reactions that occurred were limited to those reported previously with lovastatin or cholestyramine. Other lipid-lowering agents were not administered concomitantly with lovastatin during controlled clinical studies. In uncontrolled clinical studies, most of the patients who have developed myopathy were receiving concomitant therapy with immunosuppressive drugs, gemfibrozil, or niacin (nicotinic acid) (see WARNINGS, *Skeletal Muscle*).

Uncontrolled Clinical Studies: The adverse experiences observed in uncontrolled studies were similar to those seen in controlled clinical studies. Abnormal liver function tests were observed at a higher incidence than in the controlled studies (see WARNINGS, *Liver Dysfunction*). Myopathy (myalgia with marked CPK elevations) was reported in approximately 0.5% of patients (see WARNINGS, *Skeletal Muscle*).

Causal Relationship Unclear: *Nervous System*: Peripheral neuropathy has been reported, the relationship to lovastatin is uncertain. Visual evoked response, nerve conduction measurements, and electromyography in over 30 patients showed no evidence of neurotoxic effects of lovastatin.

Eye: Lens opacities (see CLINICAL PHARMACOLOGY, *Clinical Studies*).

Post-marketing Experience: Additional adverse experiences occurring since the drug was marketed are listed below.

Clinical Adverse Experiences

Gastrointestinal: Hepatitis, cholestatic jaundice, anorexia, vomiting.

Hypersensitivity Reactions: An apparent hypersensitivity syndrome has been reported rarely which has included one or more of the following features: anaphylaxis, angioedema, lupus-like syndrome, polymyalgia rheumatica, vasculitis, thrombocytopenia, leukopenia, hemolytic anemia, positive ANA, ESR increase, arthritis, arthralgia, urticaria, asthenia, photosensitivity, fever, chills, flushing, malaise, and dyspnea.

Nervous System/Psychiatric: Psychic disturbances, including anxiety, paresthesia.

Skin: Erythema multiforme, including Stevens-Johnson syndrome, toxic epidermal necrolysis.

Causal Relationship Unknown

Eye: Progression of cataracts (lens opacities).

Gastrointestinal: Pancreatitis, stomatitis.

Skin: Alopecia.

Nervous System/Psychiatric: Depression, insomnia.

Metabolic: Edema.

Clinical Laboratory Test Findings

Liver Function Tests: Liver function test abnormalities, including elevated alkaline phosphatase and bilirubin.

Thyroid Function Tests: Rare reports of thyroid function test abnormalities in patients taking concomitant thyroxine.

OVERDOSAGE. The oral LD_{50} of MEVACOR in mice is 20 g/kg.

Five healthy human volunteers have received up to 200 mg of lovastatin as a single dose without clinically significant adverse experiences. A few cases of accidental overdosage have been reported, no patients had any specific symptoms, and all patients recovered without sequelae. The maximum dose taken was 5 to 6 g.

Until further experience is obtained, no specific treatment of overdosage with MEVACOR can be recommended.

The dialyzability of lovastatin and its metabolites in man is not known at present.

DOSAGE AND ADMINISTRATION: The patient should be placed on a standard cholesterol-lowering diet before receiving MEVACOR and should continue on this diet during treatment with MEVACOR. MEVACOR should be given with meals.

The recommended starting dose is 20 mg once a day given with the evening meal. The recommended dosing range is 20 to 80 mg/day in single or divided doses; the maximum recommended dose is 80 mg/day. Adjustments of dosage should be made at intervals of 4 weeks or more. Doses should be individualized according to the patient's response (see Tables I to IV under CLINICAL PHARMACOLOGY, *Clinical Studies* for dose-response results).

For those patients with severely elevated serum cholesterol levels (i.e., >300 mg/dL [7.8 mmol/L] on diet), MEVACOR may be initiated at 40 mg/day.

In patients taking immunosuppressive drugs concomitantly with lovastatin (see WARNINGS, *Skeletal Muscle*), therapy should begin with 10 mg of MEVACOR and should not exceed 20 mg/day.

Cholesterol levels should be monitored periodically and consideration should be given to reducing the dosage of MEVACOR if cholesterol levels fall below the targeted range.

Concomitant Therapy: Preliminary evidence suggests that the cholesterol-lowering effects of lovastatin and the bile acid sequestrant, cholestyramine, are additive.

Dosage in Patients with Renal Insufficiency: In patients with severe renal insufficiency (creatinine clearance < 30 mL/min), dosage increases above 20 mg/day should be carefully considered and, if deemed necessary, implemented cautiously (see CLINICAL PHARMACOLOGY and WARNINGS, *Skeletal Muscle*).

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Biomedical Science

The AIDS Virus
What We Know and What We Can Do About It

FLOSSIE WONG-STAAL, PhD, *La Jolla, California*

Presented at the annual meeting of the Western Association of Physicians, Carmel, California, February 6-7, 1991.

Infectious diseases have long been the scourge of humanity. In the past few decades, tremendous medical advances have been made, leading to a complacency that mortality from infectious diseases is no longer a major concern. That optimism was shown to be premature, however, with the appearance of the acquired immunodeficiency syndrome (AIDS) as the epidemic of the century. In certain areas of the world, AIDS is literally wiping out entire populations.

The causative agent of AIDS, the human immunodeficiency virus (HIV), is a retrovirus. It is not the first retrovirus shown to cause disease in humans. Several years before, the first human retrovirus to be isolated was identified as the causative agent of an aggressive leukemia called adult T-cell leukemia. To date, the four human retroviruses that have been isolated and characterized all share one major feature, the propensity to infect T cells. For this reason, they have sometimes been referred to as human T-lymphotropic viruses (HTLVs). These viruses also fall neatly into two subgroups: the leukemia viruses, HTLV-I and HTLV-II, and the immunodeficiency viruses, HIV type 1 and HIV type 2. The prototype AIDS virus, HIV-1, probably originated in Central and East Africa, but it is now found in most of the world. Also associated with AIDS, HIV-2 is still largely confined to countries of western Africa.

This presentation will pertain predominantly to HIV-1, although much of it should also be relevant to HIV-2. There may be interesting parallels to be drawn from and to the leukemia viruses as well.

Pathophysiology of the Acquired Immunodeficiency Syndrome

The clinical spectrum of HIV infection is broad, affecting as it does almost all parts of the human body. The resulting symptoms reflect three major manifestations:

- The immune system is profoundly impaired. As a result, a variety of agents are able to produce opportunistic infections.
- The human immunodeficiency virus also infects the brain, resulting in central nervous system disorders, including dementia.
- Hyperproliferative disorders (hyperplasia and neoplasia) are increased in incidence, the most notable example being Kaposi's sarcoma, the incidence of which is increased about 1,000-fold in certain HIV-infected populations.

The role of HIV in associated neoplasias is probably indirect as HIV does not infect and transform these tumor cells. Indirect mechanisms, such as the action of diffusible viral or viral-induced protein, may initiate the uncontrolled hyperproliferation and eventual malignant transformation. On the other hand, the immune and neurologic manifestations of AIDS probably relate to the nature of the two types of target cells of the virus. The early target is a cell of the monocyte-macrophage lineage. This includes monocytes in the peripheral blood, Langerhans' cells, follicular dendritic cells, and microglial cells. These cells are refractory to the cytotoxic effect of the virus and therefore may serve as reservoirs for it. Furthermore, a cell of this lineage infected in the peripheral blood could migrate to different tissue sites, including the brain, where it finds sanctuary and becomes refractory to the immune surveillance of the host. The mechanisms by which primary central nervous system disorders are produced so far remain unknown.

The other major target for HIV is the T-helper cell. In fact, the antigen that defines this cell, the CD4 antigen, is the specific receptor for HIV. The receptor for HIV in monocytes is also CD4, of which a low level is sufficient for viral infection.

The $CD4^+$ lymphocyte has been compared to the maestro of an orchestra because it is the critical cell for all immune regulation. Infection with HIV severely depletes the number of these cells. When it was first observed that HIV can kill the CD4 or T4 cells in vitro, the mechanism of this depletion seemed clear. My colleagues and I observed, however, that in an infected person, only a small percentage of the cells is actually infected and expressing virus. Therefore, a direct cytopathic effect of the virus on cells may contribute to, but does not fully account for, the global and quantitative T4-cell depletion in patients with AIDS. Other alternative mechanisms have since been invoked.

A possible mechanism is that the infected cells, by virtue of the expression of the viral envelope, can adhere to uninfected cells that express the CD4 receptor. Such an interaction may result in the formation of large syncytia involving both infected and uninfected cells. The cells in such syncytia

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From the Departments of Medicine and Biology, University of California, San Diego, School of Medicine, La Jolla, California.
Reprint requests to Flossie Wong-Staal, PhD, Department of Medicine, 0613-M, University of California, San Diego, 9500 Gilman Dr, La Jolla, CA 92093-0613.

ABBREVIATIONS USED IN TEXT

AIDS = acquired immunodeficiency syndrome
AZT = zidovudine
HIV = human immunodeficiency virus
HTLV = human T-lymphotropic virus
LTR = long terminal repeat
mRNA = messenger RNA
NF_{RRE} = nuclear factor that binds to RRE
RRE = *rev* response element
SIV = simian immunodeficiency virus
SIV_{mac} = macaque strain of SIV
SIV_{sm} = sooty mangabey strain of SIV

are not able to divide or to proliferate. By this means, the replication of both infected and uninfected CD4 cells would be halted.

Circulating envelope glycoprotein gp120 can also adsorb to CD4 cells and can be taken up and processed in such a way that converts the cells into targets for cellular immune destruction. Further, there is evidence that the binding of gp120 to the CD4 molecule can activate a signal transduction pathway that decreases the expression of some cytokine products, most notably interleukin 2. This would decrease or inhibit the proliferation of T cells. Finally, a viral protein product can directly inhibit the proliferation of T cells.

Whatever the mechanism, CD4-cell depletion, the resulting impaired immune function of the host, and the progression in clinical AIDS require viral expression, replication, and the continuous recruitment of new infected cells. Soon after infection, the virus typically replicates actively and induces an antiviral response in the host. With the mounting of that immune response, viremia is suppressed, bringing on a period of clinical latency. With time, however, viremia almost invariably returns because of increased viral replication. Immune function progressively decreases, and an infected person progresses from prodromal conditions to overt clinical AIDS. These events are presented schematically in Figure 1.

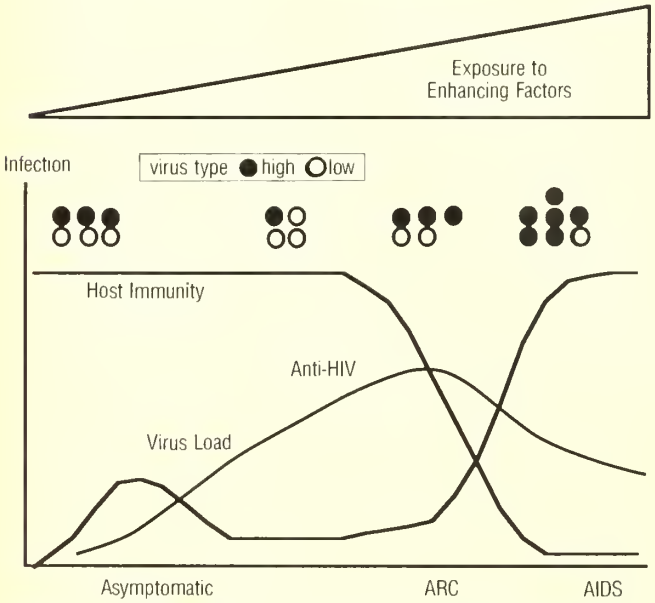

Figure 1.—The schematic shows the correlation of host immunity, virus load, and viral variation with clinical progression (see text for details). AIDS = acquired immunodeficiency syndrome, ARC = AIDS-related complex, HIV = human immunodeficiency virus

What is the cause and what is the effect? Is there more viral replication because the immune system is suppressed, or is the immune system suppressed because there is more viral replication? The answer is unclear, but both factors may pertain. The continued low replication of virus in the so-called latent period is presumably enough to erode the immune system, as a consequence of which more replicative forms of the virus can emerge. These viruses, replicating at greater efficiency, cause greater damage to the immune system, which in turn allows for the emergence of even more rapidly replicating virus. The resulting vicious spiral can account for the rapid disease progression in the later course of infection. Other determinants can also facilitate disease progression, namely the exogenous and environmental factors that can enhance viral expression. These factors include stress, exposure to UV light (which is known to activate the virus), other DNA damaging agents, and opportunistic infections of other viral agents—such as the leukemia viruses, HTLV-I and HTLV-II, the herpesviruses, and hepatitis virus—that are able to activate the expression of HIV. Furthermore, immunosuppressive agents can also contribute to AIDS progression. These can be considered as cofactors for AIDS induction. It is unlikely, however, that other than HIV, any other cofactors are essential; rather, a multitude of factors can facilitate disease progression.

Of central importance is the conclusion that viral expression and host immunity are opposing forces that determine AIDS progression. This provides a rational basis for both antiviral therapy and immunotherapy. Inducing a high level of immunity against the virus before the establishment of infection to prevent infection is the rationale for developing a vaccine.

The Replication Cycle of Retroviruses as Target for Therapy

Because HIV is a retrovirus, any inhibitors that would suppress retroviral replication would be suitable or possible anti-HIV agents. The typical retrovirus is a rather simple genetic entity, consisting of only three genes, the *gag*, *pol*, and *env* genes. The *gag* gene encodes for proteins that form the capsid of the particle, the *pol* gene encodes three separate proteins with four enzyme activities that are necessary for the replication of the virus, and the *env* gene encodes the envelope proteins that form both the surface glycoprotein and the transmembrane protein. Expression of all of these viral gene products is regulated by the interaction of cellular factors with the virus long terminal repeat (LTR). Infection begins with the binding of the viral envelope to the cellular receptor, which then allows entry of the viral core containing the RNA genetic information. A viral enzyme, reverse transcriptase, converts the RNA to DNA provirus, which can then move to the nucleus, where it is integrated into the host chromosomal DNA, catalyzed by another viral enzyme, integrase. When the virus thus becomes a permanent endowment of the host chromosome, the infection is established and cannot be cured; only viral expression can be suppressed. The integrated provirus serves as a template for messenger RNA (mRNA) that can then be processed and translated into precursor proteins. The proteins then assemble and incorporate the genomic RNA to form virion particles. The maturation of these particles requires processing of the precursor proteins, using yet another viral enzyme, protease.

Every step in this replication cycle is a possible target for

antiviral therapy. Logically, the easiest targets to focus on are the specific viral enzymes that are essential for replication. The most effective treatment so far of HIV infection is zidovudine (AZT), which is a nucleoside analogue directed at the reverse transcriptase. There are limitations to the success of AZT because of its high toxicity and the possibility of the emergence of AZT-resistant mutants in the course of treatment. This underscores the importance of seeking additional means of therapy. This would allow combined regimens that might lower the toxicity, lessen the chance of the emergence of resistant mutants, and increase the antiviral potency.

The steps described above are general strategies for inhibiting retroviral infections, but there have been few successes in inhibiting retroviral diseases, even though retroviruses have been known since the beginning of this century to be associated with a variety of diseases in animals. Recent work on AIDS has actually provided guidance for other systems. For example, AZT now can be used in feline leukemia, which is another retrovirus-induced disease.

CD4 and Infection With the Human Immunodeficiency Virus

There are also unique strategies for therapy against HIV. For example, the receptor of HIV infection is the CD4 molecule. It could be possible to exploit this information to develop antiviral drugs. Indeed, such possibilities have stirred some early excitement concerning the potential benefits of such drugs.

The CD4 molecule, a protein of the immunoglobulin family, contains variable transmembrane and cytoplasmic domains. The binding site for the virus has been mapped to the first variable domain of this molecule. Soluble fragments of CD4 that retain the binding site for the virus but lack the transmembrane and cytoplasm domains have been used as competitive inhibitors for virus infection. Specifically, soluble CD4 binds to the envelope protein (gp120) of the virus and prevents it from binding to the intact cellular receptor. There are variations of this scheme. For example, anti-idiotypic antibodies that would mimic the soluble CD4 would also compete for the binding. Binding a toxin molecule to the CD4 molecule can specifically target the toxin to destroy virus-expressing cells.

Soluble CD4 is now in clinical trial. Although it does not seem to have significant toxicity even at high doses, it also does not have demonstrable efficacy. Among a number of inherent problems for CD4 therapy, the most formidable is that of pharmacokinetics. Soluble CD4 is rapidly cleared from the circulation by the kidney, such that its levels are likely to be insufficient. Furthermore, most clinical isolates of HIV seem to be much more refractory to inhibition by soluble CD4 than are laboratory passaged isolates. Therefore, the effective level of CD4 is even more difficult to attain.

There are methods to refine this approach and to increase the stability of the CD4 molecule. For example, chimeric immunoadhesion molecules with one chain of the antibody coupled to a fragment of CD4 have been constructed to produce greater stability. Whether the refinement is sufficient to do the job remains to be seen.

If CD4 is not likely to be the magic bullet, where else can we look? The genome of HIV is much more complex than that of the usual retrovirus. Not only is the virus itself more complex, but the mechanisms that the virus uses to regulate its expression are also completely novel. Research in this area will provide new insights into eukaryotic gene regulation that will have broad implications for all biology. Moreover, the means to control infection may ultimately come from understanding the complexity and the regulatory mechanisms of the virus.

HIV Regulatory Genes

The first indication that not all retroviruses are as simple as *gag*, *pol*, and *env* came from the studies of the human leukemia viruses where additional coding information for at least two regulatory genes, *tax* and *rex*, is found. For the HIVs, the complexity is greater, with at least six extra genes (Figure 2). Several of these genes are completely dispensable for viral replication and may exert a modest effect on viral production, transmission, and perhaps tropism. Their mechanisms of action or their in vivo role in pathogenesis are not well understood at present. This review will focus on two genes, *tat* and *rev*, because they are essential for viral replication. There is a division of labor for *tat* and *rev*. The *tat* gene regulates the expression of all viral genes, and *rev* is a differential activator. Its expression is required only for the production of viral structural products, such as the *gag*, *pol*, and *env* proteins, but not for the regulatory genes themselves. Interestingly, human leukemia viruses have analogous genes to carry out the same functions. The *tax* gene for HTLV is like *tat* in its overall control of virus gene expression, and the *rex* gene, amazingly, has exactly the same function as *rev* even though the two genes have no sequence homology. Indeed, *rex* can even substitute for *rev* in activity.

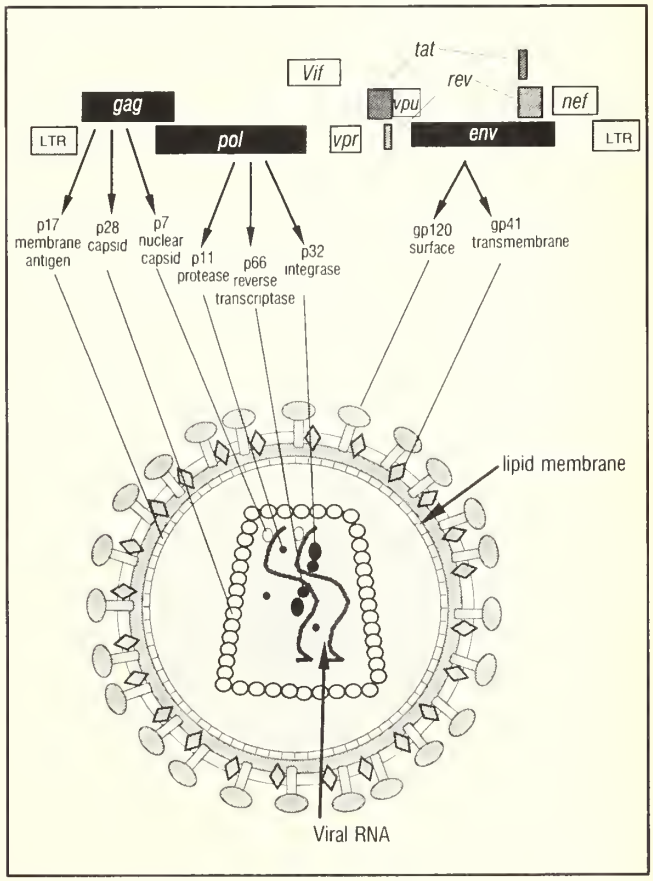

Figure 2.—The structure of the human immunodeficiency virus is shown. LTR = long terminal repeat

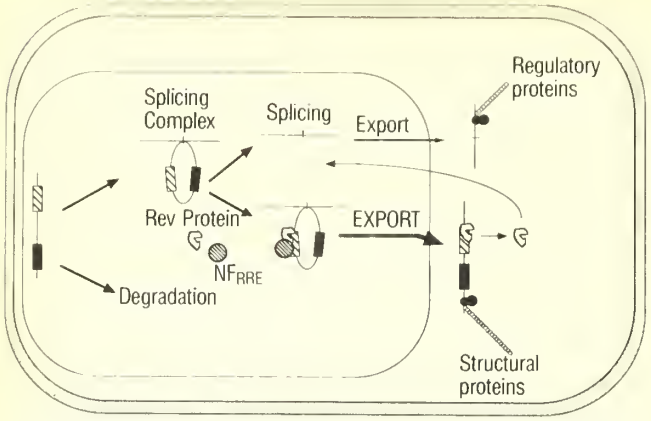

Figure 3.—The schematic shows the mechanisms of Rev function. *cis*-Repressive sequence (CRS)-containing RNA may be preferentially trapped in a spliceosome complex in the nucleus. Rev protein binds to the *rev* response element (RRE), thereby disengaging the RRE/CRS-containing RNA from the spliceosome complex and directing its export into the cytoplasm. Once in the cytoplasm, Rev can dissociate from the RNA, binds to B23 protein, and shuttles back to the nucleolus, where it is stored until recruitment by nuclear RRE-containing RNA. The nuclear factor NF_{RRE} also binds to RRE in the nucleus, but its subsequent fate has not been determined.

Through the interplay of these two genes, the human retroviruses have developed a strategy to regulate their expression either coordinately or in a temporal and differential manner. In the early phase of infection, only the regulatory genes are expressed, but in the late phase the full complement of viral proteins is made, including those that are essential for the production of viral particles. This switch from early phase to late phase is not seen in most retroviruses, and because it is brought about by the differential processing of a single primary transcript, is distinct from the early to late switch found in DNA viruses.

The regulatory proteins of HIV are encoded by small, multiply spliced RNAs, whereas the structural proteins are expressed from larger RNAs, which are either unspliced or singly spliced. The control of gene expression is divided in that *tat* is needed to turn on the gene expression of both classes of gene products, while the transition from early to late is mediated by the *rev* gene product. In a single round of viral expression, the first mRNA species that appear are the multiply spliced low-molecular-weight RNAs, with a transition to express the higher molecular weight forms in 17 to 24 hours. A mutation in *tat* results in no viral expression at all. In contrast, with a mutation in *rev*, viral mRNA is expressed, but only the lower molecular weight, multiply spliced RNAs are detected in the cytoplasm.

Although the mechanism of Rev action has not been defined, it clearly represents a novel pathway of posttranscriptional regulation. Most precursor mRNAs expressed from cellular genes follow one of two fates: they either form a spliceosome complex and get spliced and exported into cytoplasm, or they turn over in the nucleus. The Rev protein, by interacting with a specific target sequence contained in the intron of the viral precursor mRNA, is able to disengage the RNA from the spliceosome and facilitate export into the cytoplasm (Figure 3). By doing so, Rev actually diverts the distribution of multiply spliced RNA to unspliced or less spliced forms, so that Rev functions at the expense of its own production and the production of the other regulatory proteins, such as Tat. This is a way for the virus to allow a quick burst of replication and then to revert back to a more controlled steady state.

The mechanism of *tat* function is equally complex. A lot of activities have been attributed to this protein, all of them resulting in the activation of gene expression from the viral LTR. The target sequence that *tat* recognizes is called TAR, located immediately downstream of the site of transcription initiation. The *tat* gene has been known to increase the frequency of transcriptional initiation and to act as a processivity factor for transcriptional elongation (Figure 4). There is some evidence that Tat may also work as a posttranscriptional activator. The best evidence for this comes from the *Xenopus laevis* oocyte system in which it was shown that preformed mRNA injected into the nucleus can respond to *tat* transactivation.

Despite these differences in functional mechanisms, *tat* and *rev* also have several parallel features. They are both small nucleoproteins that are found predominantly in the nucleolus. Both of them recognize RNA rather than DNA targets, a feature that distinguishes them from most other viral transactivators. The target for *rev* is called the *rev* response element, or RRE, and the target for *tat* is TAR. In both cases, the RNA targets are highly structured molecules, and the recognition of them by the viral transactivators is largely structural. The *rev* gene product binds to a specific "hammerhead" (stem-loop II) region of the RRE, and *tat* binds to three unpaired bases in the so-called bulge of TAR. That binding of these viral transactivators to their target RNAs is not sufficient for function and that cellular factors are also involved are evident because mutants of both proteins that are fully capable of binding to their targets may not be functional. For example, the domain for binding to RRE has been mapped on the Rev protein. This region also doubles as the nucleolar targeting domain. In addition, there is another critical domain in which mutations do not affect the capability of the protein to bind to RRE, and yet the resultant proteins are completely inactive. Moreover, they display a negative dominant phenotype; that is, they can inhibit the function of wild-type Rev protein. It is proposed that this region is an activator domain that mediates interaction of the Rev protein with cellular factor(s). Essential functional domains including the regions for RNA binding or nuclear localization have also been mapped on the Tat protein.

An important dividend of these observations is that these viral proteins and mRNA molecules allow us to fish out cellular factors involved in their respective activities, factors that are likely to be involved in novel mechanisms of eukaryotic gene regulation and that are otherwise inaccessible. One of the major focuses in my laboratory at present is to examine several of the factors that may be involved in the *tat* and *rev* transactivation pathways. We have identified a nuclear factor, NF_{RRE}, that specifically binds to the same hammerhead structure of the RRE molecule that Rev binds. Furthermore, NF_{RRE} can bind simultaneously with Rev in close proximity, with possible further protein-protein interaction in the infected cell. This nuclear factor is highly conserved and is widely distributed in mammalian cells but absent in the *X laevis* oocytes. Interestingly, Rev is active in most cell types but not in *X laevis* oocytes. Preliminary studies showed that if partially purified NF_{RRE} protein is injected into the oocytes, Rev activity is indeed restored. Thus, NF_{RRE} is likely to have a role in *rev*-mediated transactivation. We have just cloned the NF_{RRE} gene, and it would be interesting to determine not only

what its exact role is in *rev* function but also what its role is in eukaryotic gene regulation.

Similarly, not one but several cellular factors have been shown to bind to either Tat or TAR. For example, a 68-kilodalton (kd) protein that recognizes the loop sequence of the TAR region has been described. A 45-kd protein with the same TAR-binding specificity is prevalent in T cells. A similar-sized protein binds specifically to the stem between the loop and the bulge (Figure 4). Again, it would be interesting to determine the functions of these proteins in both the infected and uninfected cells.

As noted, *tat* and *rev* are both required for viral replication and therefore play important roles in the pathogenesis of HIV. In addition, the potential effects of these molecules, particularly for Tat, may go beyond their role as viral transactivators. There is now evidence that Tat may act as an exogenous factor. It can be released from infected cells or Tat-producing cells and be found in the extracellular medium. Exogenous Tat can also be taken up by uninfected cells in a functional form—that is, the internalized Tat retains its ability to transactivate its target, the LTR. Therefore, its sphere of action is not restricted to the infected cell. Also, its target is not restricted to the viral LTR. A first demonstrated example of Tat activating a heterologous promoter is that of the JC virus late promoter, suggesting that along with immune suppression as a consequence of HIV infection, Tat may contribute to the reactivation of latent JC virus infection. This may lead to the induction of the neurologic disorder, progressive multifocal leukoencephalopathy, associated with active JC virus infection. Furthermore, Tat may have a greater effect on cellular function than we had previously thought, as it was also found recently to activate some cytokine genes, specifically the transforming growth factor-β gene.

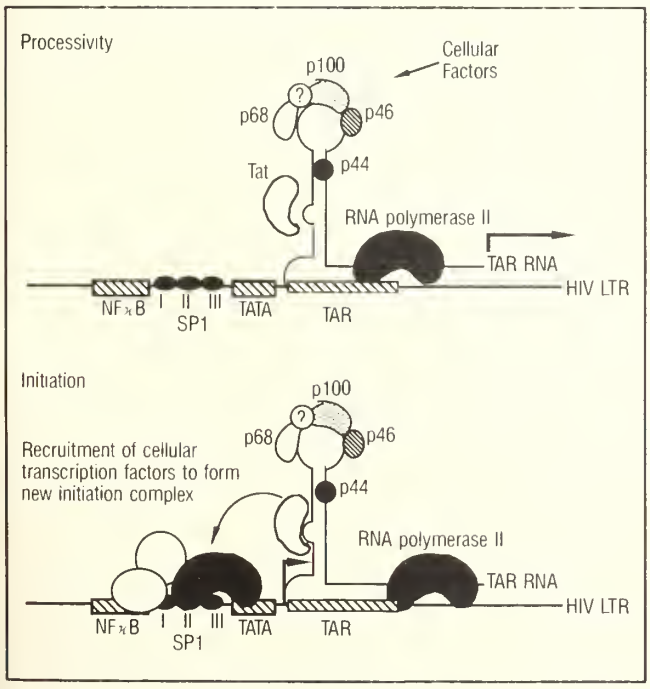

Figure 4.—The mechanisms of Tat activation are shown. Tat has been proposed to increase the processivity of transcription or the frequency of initiation. The role of various cell factors that bind to the target sequence, TAR, in either mechanism has not been defined. HIV LTR = human immunodeficiency virus long terminal repeat

Exogenous Tat protein can apparently modulate cell growth. It specifically suppresses antigen-activated T-cell proliferation and increases the proliferation of cells derived from Kaposi's sarcoma-derived cells. These activities can contribute to immunosuppression and to the progression of the Kaposi's sarcoma tumors in HIV-infected persons.

The remarkable parallels between HIV and HTLV have often prompted workers in both areas to take cues from each other. An illustration of this point comes from recent investigations of the Tax protein of HTLV. Analogous to the observations on Tat, Tax is found extracellularly, can be internalized in a functional form, and can activate T cells through the NFκB pathway and stimulate their proliferation. These features of Tax are in line with the pathogenic potential of the leukemia viruses, which is T-cell activation and transformation.

Regulatory Genes as Possible Targets

Because the *tat* and *rev* genes are important for viral replication and pathogenesis, a useful antiviral strategy obviously would be to interfere with their functions. A straightforward way has been to inhibit the expression of both genes using antisense oligonucleotides directed at the *tat/rev* coding region. Indeed, viral expression can be specifically inhibited by such compounds, as measured by expression of the core protein p24 or viral reverse transcriptase. The sense-strand of the same sequence had no effect. When the expression of RNA is examined in the antisense-treated cells, neither *tat* nor *rev* is completely inhibited—that is, some RNA, including singly spliced viral RNA, is expressed. The unspliced genomic RNA, however (the *gag-pol* message), appears to be highly sensitive to *rev* depletion and is completely repressed. As a result, viral production is also repressed. Therefore, even though the antisense approach is not an efficient means of gene inhibition, viral production can be completely repressed in the absence of total gene inhibition, making the *rev* gene an attractive target for virus inhibition.

As discussed earlier, both *tat* and *rev* transactivations involve a number of players: the viral protein, a viral RNA element, and cellular factors, each interacting with the others. It is possible to devise means of interrupting those interactions that are crucial to their functions. For example, some mutant proteins are negative dominant. These proteins can retain binding activity to their RNA targets but are not able to interact with the proper cellular factors and therefore would not function. They can thus act as competitive inhibitors of the wild-type protein. Alternatively, oligonucleotides that can hybridize to the stem-loop sequences of the RNA target can presumably disrupt the structure or the folding of these molecules, thereby rendering them incapable of interacting with both viral and cellular factors. Synthetic oligonucleotides directed at regions of RRE that have previously been shown to be important for *rev* function have been used. As a control, oligonucleotides complementary to a dispensable loop in RRE were used. All the antisense oligonucleotides directed at the critical regions were capable of inhibiting *rev* activity and viral production, but the control oligonucleotides directed at the dispensable loop, as well as random-sequence oligonucleotides, were not inhibitory (M. Klotman, S. Daefler, F. Wong-Staal, unpublished data, 1991).

There are many variations on this theme. One example is

the expression of multiple copies of TAR RNA as a decoy to compete with normal TAR in the virus genome for expression. A potential problem of expressing a TAR or RRE decoy, however, is that it may also sequester cellular factors that may be important for cell function. To overcome this problem, a vector has been devised in which the expression of TAR is conditional on *tat* acting on its promoter, which is the HIV LTR. Therefore, these decoy molecules would only be expressed in infected cells, where the first sign of the expression of *tat* can then unleash a whole army of these TAR decoys to limit the extent of viral replication (J. Lisziewicz, MD, written communication, April 1991).

The foregoing discussion only relates to laboratory successes on inhibiting viral functions. This is a far cry from turning them into pharmaceutic products. Many considerations are important in drug development: toxicity of the compounds, pharmacokinetics, and cost effectiveness, to mention only a few. Moreover, the major recurrent difficulty is to have continuous delivery of these agents to maintain a persistent high level in the bloodstream or appropriate target tissues. In this sense, these novel antiviral approaches should dovetail ultimately with the development of gene therapy, which is itself a rapidly evolving field and which may have finally come of age.

The Potential for Vaccine Development

Optimism for the prospects of an AIDS vaccine has waxed and waned since the discovery of the virus. There are two major hurdles for the development of an HIV vaccine: the lack of an appropriate animal model; and the diversity of the virus, which makes it questionable whether it is feasible to develop a broadly cross-reactive vaccine. Lately there is renewed optimism because substantial progress has been made relating to both issues.

A candidate vaccine would have to be evaluated in an animal model where protection from infection can be verified. For HIV-1, the only animals other than humans that can be infected are chimpanzees and apes. Because these primates are on the endangered species list, it is hard to get sufficiently large numbers for vaccine evaluation. Furthermore, these animals do not get AIDS with HIV-1 infection. It is not known if they are appropriate models because their immune responses may be different from those in humans.

The simian model may be better. A number of Old World monkeys are naturally infected with a virus similar to HIV-1, designated the simian immunodeficiency virus (SIV). Four groups of primate immunodeficiency viruses have now been identified: HIV-1 and rare viruses identified from chimpanzees *(Pan troglodytes);* viruses isolated from African green monkeys *(Cercopithecus sabaeus);* viruses from mandrills *(Mandrillus mormon);* and those isolated from sooty mangabey monkeys *(Ceroccebus fuliginosus)* (SIV_{sm}), the West African virus HIV-2, and SIV isolated from captive macaque monkeys (*Macaca* species) (SIV_{mac}). Because the sooty mangabey monkeys, but not macaques, are prevalently infected in the wild, it is thought that HIV-2 and SIV_{mac} might have actually been derived from a cross-species infection of (SIV_{sm}) or a virus closely related to it. All four groups are at about equal distance from each other.

The monkeys that have been infected in the wild have a high prevalence of infection (30% to 50% of African green monkeys are seropositive for SIV) but do not become sick. This suggests a coadaptation of the virus and host in the course of evolution. The same virus when inoculated into macaques, which are naive animals, induces a disease much like AIDS. Type 2 HIV must have entered the human population recently, and it causes disease. Macaques are also susceptible to AIDS induction by some HIV-2 strains. The macaques then provide a relevant model that is a bit more accessible.

Progress has been made in the simian model. Most important, immunization with killed virus preparations protects against a challenge infection by SIV. Even in some cases where vaccination had not protected against infection, it seemed to protect against disease. This may be the best that we can hope for from an AIDS vaccine. Previous infections with nonpathogenic variants can also protect against disease induction by the more virulent forms of virus.

Thus, we are encouraged that in principle a vaccine against this group of viruses can work. Because of its potential hazards, a vaccine made from intact inactivated virus is not one of choice, however. Most investigators are focusing on using viral subunits for an HIV vaccine. The added advantage of this approach is that correct epitopes can be chosen and the wrong ones excluded. For example, the envelope for HIV contains a number of "good epitopes": neutralizing epitopes and epitopes that would elicit cellular immunity. There are also "bad epitopes," namely, those that elicit enhancing antibodies, immunosuppressive epitopes, and epitopes that may induce autoimmunity by molecular mimicry.

The region on the HIV envelope that is the most potent for eliciting neutralizing antibodies has been sublocalized to a peptide of about 20 amino acids. This region contains the principal neutralizing epitope(s). Not only can peptides derived thereof induce high-titer neutralizing antibodies, but they can also adsorb most of the neutralizing activities elicited by the whole envelope. That recombinant proteins or synthetic peptides were effective in eliciting a potent neutralization response created much excitement and suggested the feasibility of a synthetic peptide vaccine approach. The same envelope region also contains a cytotoxic T-cell epitope, suggesting that this region may turn out to be the Achilles' heel of the virus. Enthusiasm was greatly dimmed, however, when this region of the viral envelope was found to map into a highly variable region, now referred to as V_3 or the third hypervariable stretch on gp120. The V_3 sequence potentially forms a loop by a cysteine-cysteine disulfide bridge.

The antigenic region of this loop has been mapped to close to the crown of the sequence. In fact, a synthetic peptide that comprises the sequence only at the crown has also been shown to elicit high titers of neutralizing antibodies.

Antibodies directed at this peptide were initially thought to be strictly type-specific; that is, they would not cross-neutralize any heterologous strains. This assessment has turned out to be unduly pessimistic. An alignment of the V_3 loop among the dozen or so published sequences of HIV revealed that the early prototypes that were used (HXB-2, LAV, and RF) are rare representatives of the universe of HIV. The sequences of hundreds of isolated HIV organisms have now been determined, of which about 30% have a common consensus sequence (with the MN virus) at the tip of the V_3 loop. Another significant fraction shares seven out of nine of these residues. The early prototypes (III-B, LAV, and RF) were rarely represented. More important, antibodies to the MN peptide now can block the infectivity of many of these organisms. These results raise the possibility that a cocktail

of the right representation of V_3-derived sequences may be incorporated into a broadly cross-reactive vaccine.

In conclusion, the principles of a vaccine have been shown to work. Now we need to confirm and extend these observations and put them into practice.

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Articles

Decision Making in Critically Ill Patients With Hematologic Malignancy

STEPHEN W. CRAWFORD, MD, *Seattle, Washington*

Hematologic neoplasms that were previously considered fatal are now potentially curable with techniques such as bone marrow transplantation. Such therapies also carry significant morbidity and mortality. With the increasing application of these therapies, a growing number of physicians are using medical decision making regarding critical care for these patients. The process by which ethical decisions are reached for these critically ill patients may be baffling because of several factors: rapidly evolving treatments, uncertain probabilities of the cure of the malignant disorder, the relatively young age of many of these patients, and the poor prognosis with critical illness. I discuss a process to reach acceptable decisions, providing a case example of the application of the process. This process is derived from the ethical principles that drive decision making in general medicine and attempts to maximize patients' autonomy. It involves a consideration of accurate information regarding the disease process and the prognosis, a clear delineation of the goals of the medical care, and communication with patients. Appropriate, ethical, and consistent decisions regarding the critical care of patients with hematologic malignancy can be reached when these considerations are addressed.

(Crawford SW: Decision making in critically ill patients with hematologic malignancy. West J Med 1991 Nov; 155:488-493)

Because of advances in treatment, such as marrow transplantation, a growing number of physicians are faced with decisions regarding withholding and withdrawing life support for patients with hematologic malignancy.[1] The treatment of hematologic malignancy poses problems in decision making uniquely distinct from many areas of medicine. These patients are faced with near-certain death without treatment. The treatments themselves, however, are life-threatening while being potentially lifesaving. How far are these treatments to be extended in balancing the possible threat to life with the likelihood of cure? A firm understanding of the decision-making process for critically ill patients is imperative for the rational and consistent care of these patients. In this article I will address the process by which these decisions can be achieved.

The prognosis for patients with hematologic malignancy who become critically ill has historically been poor.[2-4] The dismal prognoses have prompted the recommendation that intensive life support for patients with malignancy is not ethically appropriate: it approaches futility and applies medical resources wastefully. New therapies, such as bone marrow transplantation and biologic response modifiers, offer the possibility of a cure of hematologic neoplasms and other fatal diseases. These patients are often provided heroic levels of care in the hope that life support (including mechanical ventilation) will allow them to survive treatment and return to normal function.

Despite the hopes for cure that attend these treatments, anecdotes suggest that the survival of critically ill patients with hematologic malignancy is infrequent but not unprecedented. Only recently have data regarding the outcomes of marrow transplant recipients been available.[5,6] These data confirm the anecdotes. Long-term survival for marrow recipients requiring assisted mechanical ventilation is about 5%. Unfortunately, similar data are not available for other recent advances in oncologic therapy. Thus the question arises: on what bases are the decisions to provide (or continue) life support to critically ill patients undergoing treatment for hematologic malignancy made?

Ethical clinical decisions can be reached in these cases if they are made in the context of accepted ethical principles. The decisions are made on the basis of accurate information regarding the disease process and the prognosis, a clear delineation of the goals of the medical care, and input from the patient. Acceptable decisions regarding life-sustaining therapies can be reached when attainable goals and patients' wishes are clearly identified. To this end, accurate information regarding disease processes and prognoses is crucial to establishing realistic goals and informing patients of possible interventions and outcomes.

Goals of Medical Care in Oncology

The goals of care in patients with hematologic malignancy should be common to those of medicine in general. The goals of medicine in the Western culture were expressed early in medical literature and, as stated in the Hippocratic Corpus, are the attenuation of disease, the relief of suffering, and restraint from the treatment of hopelessly ill patients (lest physicians be thought of as charlatans).[7]

Throughout most of history, there was little that medicine could offer to alter the outcome of disease. The principal endeavors of medicine were to provide diagnoses, prognoses, and supportive care. Modern advances in anesthesia, surgical technique, antisepsis, antibiotics, and vaccines have changed the capabilities of medicine, and modern society has altered its expectations. Because medical technology now permits us to alter disease processes, Western society has imposed additional goals on medical providers. The attenua-

From the Division of Clinical Research, Fred Hutchinson Cancer Research Center, and the Department of Medicine, University of Washington School of Medicine, Seattle.

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Reprint requests to Stephen W. Crawford, MD, Fred Hutchinson Cancer Research Center, 1124 Columbia St, Seattle, WA 98104.

tion of disease and relief of suffering, while still important endeavors, are now joined (or supplanted) by the goals of maintaining or restoring function and prolonging life.[8]

These notions that medicine can "save life" and "cure disease" are recent in human history and a reflection of scientific advances. Immunology and transplant biology represent novel extensions of our newly discovered capacities to affect the outcome of disease. Thus, while Hippocratic goals are still relevant, it is increasingly difficult to apply the last of the Hippocratic injunctions, namely, to refrain from treating hopeless cases. The question today is, what case is hopeless? For example, should the promise of cure with a successful marrow transplantation impart hope to otherwise desperate cases?

Pertinent to this example, most candidates for marrow transplantation suffer from ultimately fatal diseases. On the whole, these patients are rarely older than 50 years. For them, the goal of intervention is to cure disease, leading to the restoration of normal function and life expectancy. At the very least, it is to prolong life. These patients choose this mode of therapy with the expectation of cure. The same is true for patients receiving other novel therapies for the treatment of hematologic malignancy.

The limitations of new therapies are not known. Clearly, not all patients can or will be saved by these technologies. Experience to date is limited in both numbers of disease processes and patients treated. The patients who will not survive grave illness during treatment are difficult to identify with certainty.[5,9] Therapies to treat both the malignant disorders and the complications of the treatments are evolving rapidly. New discoveries may favorably influence the prognosis of critically ill patients with hematologic malignancy. An example of a dramatic improvement in the prognosis of a serious infection is the successful treatment of cytomegalovirus pneumonia after marrow transplantation with the newly developed antiviral agent ganciclovir.[10,11]

Given the problems posed by the relative lack of experience with specific treatment modalities for hematologic malignancy and the rapid advances in treatment-related complications, how can reproducible solutions be found for the ethical dilemmas of the care of the critically ill? Because the goals of medicine apply to patients with hematologic malignancy, it is reasonable to assume that the principles of decision making that apply to medicine in general can be adapted to the setting of advanced oncology treatment.

Considerations for Clinical Decision Making

The process of medical decision making should adhere to accepted ethical principles of the society in which the medical care is provided. *Webster's New World Dictionary* defines "ethics" as the system or code of morals of a particular philosopher, religion, or group. Thus, ethical principles are the tenets that describe what is "right" or correct behavior within a society. While each of us has an internal code of morality, a personal ethic, it is physicians' responsibility to practice medicine within the morality of the society. The fundamental principles of medical ethics in Western society have been summarized in the ideals of beneficence, autonomy, and justice. These ideals serve to protect and guarantee the rights and interests of the individual within the context of the needs of the society.

Beneficence is the principle that medical intervention should be in the best interest of the patient. Autonomy indicates that individual preferences are given high regard in decision making and that competent patients may refuse intervention. The intervention should be equitable and just, thus serving the greater interests of society.

Patients with fatal hematologic malignancy present distinct problems to the considerations of withdrawing and withholding life support. First is the relatively young age of many of these patients and the potential to return to a normal life span and function with successful treatment. Second is the potential for a significant risk of toxicity or premature death due to the treatment. Third is uncertainty regarding the probability of successful treatment or of the level of risk for an unfavorable outcome in the event of complications. These problems increase the difficulty in dealing with these patients and make it imperative that the basic ethical principles be followed in decision making.

Presentation of a Case

The patient, a 27-year-old married man, underwent allogeneic marrow transplantation for acute nonlymphoblastic leukemia in relapse. The sibling donor was mismatched with the recipient at one HLA locus. The patient was seropositive for cytomegalovirus (CMV).

He was conditioned for transplant with high-dose cyclophosphamide therapy and fractionated total body irradiation. By day 40 after transplantation, the donor marrow had engrafted with a circulating absolute neutrophil count above 1.0×10^9 per liter (1,000 per μl), but persistent thrombocytopenia necessitated frequent platelet transfusions. Early evidence of hepatic veno-occlusive disease and mild renal dysfunction was abating, and oral mucositis had resolved. A skin rash and elevated serum aminotransferase and bilirubin levels were felt to represent acute graft-versus-host disease. There was no evidence of residual leukemia.

Respiratory distress then developed, and bilateral pulmonary infiltrates were seen on a chest film. He requested, "Help me, I can't get my breath." Assisted mechanical ventilation appeared necessary as life support on the basis of his respiratory status. At this point, the patient's wife said, "I don't want him to live the rest of his life on a respirator." What were the appropriate medical decisions?

The Process of Decision Making

Defining the Goals

The pivotal point for the process of medical decision making is identifying the goal of intervention. The definition of an appropriate goal is paramount, particularly when considering the indications for proposed medical intervention. An "appropriate" goal is both consistent with the patient's aspirations and capable of being achieved. Who chooses the goal that defines the indications for treatment?

In its report on informed consent, the President's Commission for the Study of Ethical Problems concluded that the decisions about health care ultimately rest with the competent patient.[12] Therefore, all questions regarding medical decision making must be framed within the context of a patient's intent. Adult patients have the right to refuse treatment, regardless of the benevolent intent of their physicians. The physicians' recommendations for treatment, however, are made on the basis of an understanding of the goals desired by the patient. Patients' acceptance or refusal is made on the basis of the perceived burdens and risks of the intervention relative to the possible benefits.

Autonomy, or self-determination, is a crucial element in medical decision making in our society. United States court decisions have affirmed competent patients' right to refuse medical interventions. To be able to consider medical care, however, patients must weigh the options available in relation to the goals they wish to achieve. Thus, all consideration of potentially expensive, intensive, lengthy, and painful life-sustaining modalities must include the concept of "proportional treatment." Is there "in the view of the patient, . . . at least a reasonable chance of providing benefits . . . which outweigh the burdens attendant to the treatment"?[13] This question applies to patients with hematologic malignancy as well. What potential pain or inconvenience is appropriate for a patient to endure for the unknown chance of survival? What level of benefit warrants the sacrifice?

Central to the concept of proportionate treatment is the phrase "in the view of the patient." This concept requires that physicians provide patients with information regarding the anticipated risks associated with each treatment course and the probability of outcomes, so that patients may determine their preference. Physicians, as medical experts, have a responsibility to counsel patients regarding a course of treatment and to explain the attendant risks and benefits, as well as alternatives to the recommended course. Adult patients' preferences, informed by physicians' recommendations, are foremost in deciding the ultimate balance of proportionate treatment.

The initial task of a medical provider is to delineate clearly the goals of a patient so that appropriate interventions may be offered. The subsequent tasks are to inform the patient as to the probability of achieving the goal and the likely clinical course that will ensue. It would be useless to propose interventions that offer no probability of securing the patient's goal. It is the responsibility of physicians to avoid such counsel and inform patients when the goals cannot be met. On the basis of the information, a patient can agree or refuse intervention. In the oncology unit, the difficulty in this task is compounded by the lack of data regarding risks, burdens, and probability of benefit for many interventions. Without such information, a truly informed decision by a competent patient is impossible.

The patient in the example was at high risk for CMV pneumonia, and the presentation was consistent with that diagnosis. Although the mortality of this condition had been over 85%, treatment regimens with ganciclovir and immune globulins have reduced it to as low as 30%.[10,11] Respiratory failure, apparently independent of cause, may be a grimmer prognostic factor for marrow recipients. The chance of surviving beyond six months after assisted mechanical ventilation appears to be only 5%.[4] Patient characteristics and associated organ failures do not appear to be predictive of survival. Anecdotally, some marrow recipients with multiple organ failures have been long-term, disease-free survivors after receiving mechanical ventilatory support.

This man opted for the transplant with the fervent hope and expectation of a cure of his malignant disorder and a return to a functional life. He undertook the transplant with the understanding that the probability of disease-free survival was less than 20% given his disease status. His goal of treatment at this point remained unchanged from before: to cure the malignant disorder. Because potentially effective therapies existed for the most likely disease that this patient had (CMV pneumonia), this was an appropriate and achievable goal.

Medical Indications for Treatment

It has been argued that there is no imperative to provide futile medical intervention.[14] In fact, it may be appropriate to withhold interventions that are futile. The problem lies in deciding which interventions are futile. Schneiderman and co-workers have proposed that futile interventions be described as "any effort to achieve a result that is possible but that reasoning or experience suggests is highly improbable and that cannot be systematically produced."[15(p951)] To give this description quantitative value, they suggested that an intervention be considered futile if, on the basis of studies or experience, success is not achieved in 100 attempts. This description of futility provides little help to the consideration of critically ill patients with hematologic malignancy. For many of these patients, there is insufficient information on which to conclude that the rate of success is less than 1 in 100. The interventions often are too novel and the clinical situations too complex to compile a sufficient number of reference cases. Extrapolating from other disease states may not be possible given the novel treatments often used. Schneiderman and associates recognized that rare disorders may present with "insufficient experience for a confident judgment of futility."[15(p952)] In such cases, they suggest that "In judging futility, as in other matters, physicians should admit uncertainty rather than impose unsubstantiated claims of certainty."

I agree with these points, but the admission of uncertainty in these cases includes admitting ignorance regarding the certainty of the futility or of the success of the intervention. It is true that medical progress is not made through repeated futile intervention, as Schneiderman and colleagues noted.[15] In addition, progress is not made through the assumption of the futility of interventions for which insufficient experience exists. Thus, interventions should rarely be withheld solely on the basis of supposed medical futility when the intervention is either novel or experimental. This is not to deny that there may be other valid reasons for either not offering novel intervention, or for the patient not accepting it, regardless of the probability of benefit.

This lack of appropriate information regarding the prognosis and likely course of the disease in the setting of advanced treatment of hematologic malignancy is the greatest hurdle to decision making. Often the basis for medical recommendations becomes anecdotal evidence. Thus, the interventions become truly empiric—not based on scientific theory but on personal experience and bias of therapeutic value. Because there is a lack of information, oncologists should request and rely extensively on the experience and expertise of other medical specialists.

The medical indications for intervention in this case clearly depended on an accurate diagnosis of the patient's condition and a prognosis based on the best current data about the natural course of the disease and the treatment options. Confirming a definitive diagnosis was in this patient's best interest. Diagnostic efforts such as bronchoscopy with bronchoalveolar lavage were indicated.[16]

Survival from respiratory failure, should it ensue, would not be unprecedented, but it would be unlikely. Thus, it was possible but improbable. Experience at many marrow trans-

plant centers suggested that the probability of successfully treating CMV pneumonia complicated by respiratory failure was low. Since the demonstration of the beneficial effect of current therapy on the outcome of CMV pneumonia, there is reason to think that the probability of recovery from this condition is now improved. It must be admitted, however, that too little experience exists to be certain that the therapy increases the incidence of successful outcomes in the presence of established respiratory failure. It would be difficult to describe recovery as "highly" improbable or less than 1 in 100, as Schneiderman and co-workers suggest as a threshold to indicate medical futility. At this point in the patient's illness, it was not clear that the patient's goal was unattainable.

If this patient had not undergone marrow transplantation, these levels of probability would constitute futile intervention because any clinical success would be at best temporary: the patient's underlying disease would wipe out any immediate gains, and his death would be imminent. For this patient, who had received a transplant that had the potential of preserving life for a considerable period if he survived this crisis, the low (but unknown) probabilities should not be considered indicative of futility. Therefore, from the viewpoint of medical indications, critical care, including a trial period of mechanical ventilation, would be justified.

A consideration of justice plays a limited role in clinical decision making for critically ill patients with hematologic malignancy. Decisions regarding the just macroallocation of resources are not made at the individual patient level. We practice medicine within the constraints of the resources allotted by society. The microallocation of resources, however, profoundly influences decision making at the individual level. The inability to pay for potential therapy and the possibility of financial destitution of a family after expensive treatment are considerations. These "microjustice" concerns and the implication for patients and their families are best understood and decided by them, not their physicians. For these reasons, the concept of justice should be superseded by patients' autonomy in most decisions of withholding or withdrawing life support.

Patients' Preferences

In the case presented, the patient must determine the "proportion" of burden and benefit in his situation. He could not do this in a vacuum of medical information and relied on his physicians for counsel and advice.[17,18]

The patient had never explicitly discussed with his physicians his desires regarding terminating therapy. At this time he was critically ill, sedated, and depressed because of the length of his hospital stay. His mental state raised doubts regarding his capacity to participate in the decision about continued medical care and the possible requirement for ventilatory support. In the absence of direction to the contrary, it was prudent to assume on the basis of the patient's participation in the transplant program that he valued life. Medical interventions and life support were provided in an attempt to achieve the goal of curing his disease as long as it was a medical possibility. Discussion with the patient about these decisions would have been appropriate after the institution of this medical support had he recovered his ability to participate.

Experience with the acquired immunodeficiency syndrome suggests that patients want to be actively involved in decisions regarding their care.[19] Patients confronted with the prospects of mechanical ventilation for *Pneumocystis carinii* pneumonia are capable of choosing to forego this intervention.[20] In addition, patients not approached often express a wish to discuss these options with their physicians. Perhaps oncologists should routinely and explicitly discuss intensive care and mechanical ventilation with patients and families before marrow transplantation to determine patients' preferences.

Use of a Surrogate

Medical decision making for physicians is particularly difficult when a patient is mentally incapacitated. The use of an appropriate surrogate (usually the next of kin or a legally designated party) to speak for (and in the best interests of) an incapacitated patient facilitates the decision-making process but also poses difficulties. Among these, the patient must clearly be shown to be incapable of understanding the data presented and expressing his or her wishes before the autonomy of the patient is bypassed.[12] Just as a patient is assumed to opt for potentially life-saving intervention over death, the patient is assumed to be competent to participate in decision making over involving a surrogate.

The patient presented could participate in the decision-making process to the extent that he said that he was short of breath and wanted relief of this sensation. Beyond these comments, the consensus of medical opinion (including consultation with psychologists) was that he could not adequately process information and arrive at cogent decisions because of the severity of his illness. In this situation, his wife was most appropriate to act as his surrogate as she was most likely to understand his motivations and anticipate his decisions. As well, she would most likely present decisions from a position of intimate and loving concern for his well-being.

Her responsibility was not to make decisions for her husband but to relay the decisions that he would have made if capable.[12] The goals of therapy desired by the patient should direct care, provided the goals (such as cure of disease) were attainable. To this end, both the medical staff and family would have benefited from any previously expressed wishes for his care. If his wife had not known what choices he would have made, she could assist in making decisions that would serve his best interest.

The potential uncertainty of decisions and the emotional trauma to his wife in acting as a surrogate might have been avoided had the patient provided advance directives before his critical illness about the desirability of life support. In addition, the patient could have appointed another surrogate (or durable power of attorney for medical care) to make crucial decisions in his behalf.[21] Preparations like these are more likely to occur if physicians anticipate the likely medical course and discuss the possible choices for each complication in advance.[21]

Because the determination of medical facts and the interpretation of the preferences of patients and surrogates in this case were difficult, the use of an institutional ethics committee could have been helpful. These committees, now common in United States health care, do not usurp the role of attending physicians or of the patients and families.[22] These parties retain the authority to make decisions. The opportunity to discuss the medical complexities, the ethical principles, and legal implications of these decisions, however, can

be enhanced by presenting them to a knowledgeable and impartial group. The deliberations of such committees can assist the primary decision makers in seeing what is often difficult to see when closely involved in a case.

Quality of Life

The statement, "I don't want him to live the rest of his life on a respirator," by the wife of this patient likely reflected concern about his potential suffering. The exact meaning of her remark was not clear, however. Such comments by family members are unfortunately common, but whether they reflect concern for possible short-term suffering, long-term disability, or "death with dignity" issues is often vague. More important, it is not clear whether such statements reflect views and wishes of the patient or of the family.

Statements such as the one quoted should prompt frank discussion between the physician and the patient and family. The true concerns should be spelled out clearly and information regarding the possible outcomes from treatments detailed. The relative value of life (including life with disability) and the degree of discomfort or suffering a patient is willing to accept to attain that life must be explored before decisions regarding care can be reached.

There is no reason to suspect that marrow recipients who survive respiratory failure have long-term ventilatory impairment. Anecdotal experience suggests that such patients have a gradual return to normal function analogous to that seen after the adult respiratory distress syndrome in nonimmunosuppressed patients.[23] Given his respiratory failure and a lack of direction from the patient otherwise, it was appropriate to discuss the prognosis and course with the patient and his wife to allay their concerns. A therapeutic trial of ventilatory support was appropriate to permit time for diagnostic procedures to be completed. In addition, more information regarding the extent and course of his disease would become available during this trial period.

His wife concurred that such an approach was consistent with the patient's desire for cure and would be in his best interest. Assisted mechanical ventilation was instituted and bronchoalveolar lavage done. The viral immunofluorescent antibody stains and cultures were positive for CMV. Treatment with ganciclovir and CMV-specific immune globulin was begun.

Inability to Achieve the Goal

As discussed, there were few data to indicate the prognosis of respiratory failure due to CMV treated with ganciclovir. Thus, it was difficult to define if or when this would constitute futile intervention. There was an appropriate sense of urgency to arrive at a decision regarding treatment because the emotional and financial implications were substantial. Given the difficulties, it was important that the primary oncology team work closely with consulting physicians to reach a consensus regarding prognosis and treatment. A reasonable approach was the institution of a time-limited therapeutic trial of assisted mechanical ventilation and specific CMV treatment. If, in the best judgment of medical experts, reasoning and experience would suggest that treatment would have no chance of curing the disease (or the patient decided that the likely outcomes of treatment did not justify the burdens posed on him), it is reasonable that the goals of treatment must change. Such a consensus would have been reached in this case if fulminant hepatic failure, progressive respiratory compromise refractory to maximal oxygenation support, or a relapse of his leukemia were to ensue or no clinical improvement were noted after a reasonable, predetermined period of time.

Data in many subsets of critically ill patients suggest that the survival rates for such complications are less than 1%. At that point, reasonable goals would become the relief of suffering and providing suitable time for the patient and family to attend to necessary arrangements in the anticipation of death. With these goals in mind, the continuation or institution of new technologies that did not relieve suffering would be inappropriate. The new goals would dictate that comfort measures be instituted and that interventions not contributing to these ends be terminated.

The sequence of the withdrawal of support and the level of sedation and analgesia that are required vary in each case, but the goals of the actions should be clear to all involved.[17] To this end, imposing or continuing support with arbitrary limitations, such as limiting oxygen concentrations or continuing vasopressors or antibiotics at preset rates of administration, do not achieve any goals. Such actions give the appearance of medical care but are not expected either to cure the patient or to relieve suffering and do not prolong life. The continuation of "limited" medical care is contrary to the assurance of a quality life and death in many cases, unless there is another goal that will be achieved by the action. Occasionally care is continued until the patient or family has achieved a short-term goal, such as the arrival of a relative who wishes to be present.

In the case of the marrow recipient presented, pulmonary function and gas exchange continued to decline steadily over a ten-day period despite evidence of the eradication of the CMV infection. Arterial hypoxemia and increasing minute ventilation requirements necessitated 100% supplemental oxygen, high levels of positive end-expiratory pressure, and increasing respiratory rates that were inadequate to achieve physiologic blood gas values. When declining renal function ensued and hemodialysis became necessary for continued survival, a consensus of medical opinion was sought among the transplant team, pulmonary and critical care physicians, and the nephrology consultants. The conclusion was reached that there were insufficient data to state conclusively that there was no probability of survival, but the steadily declining course despite near-maximal life support made recovery highly improbable. On the basis of collective experience, it was concluded that the probable course would include continued mechanical ventilation, hemodialysis, recurrent pulmonary infections, and other complications.

Because the patient still could not participate in decision making, his wife continued to act in his best interest as surrogate. She was told of the collective medical evaluation. In light of the consensus that the goal of cure would not be reached, the alternative goal of a quiet and orderly death was recommended. At this time, she agreed that her husband would not have opted for the prolonged life support with such limited probability of survival. At that point, adequate sedation was administered to relieve any discomfort, and interventions not necessary for comfort were withdrawn. These included hemodialysis, antibiotics, blood products, and supplemental oxygen. He died quietly in the company of his immediate family.

Conclusions

This case demonstrates several important aspects of the process of decision making in cases of critically ill adult patients undergoing therapy for hematologic malignancy:

- The goals of medical care should be clearly defined before the implementation or withdrawal of treatment.
- Informed decisions regarding treatment should be made by the patient with the assistance of medical staff. Whenever possible, patients' preferences regarding life support and quality of life should be solicited before medical intervention, especially when the likelihood of the patient being incapacitated during the procedure is high.
- Physicians must possess accurate information about the prognosis, risks, and benefits of available treatments. To this end, a consensus of expert medical opinions is advisable before reaching conclusions regarding prognosis. Continued studies and the publication of critical care treatments are necessary in specific patient populations to accurately determine prognoses.
- Surrogates should not be asked to make decisions in the place of an incapacitated patient but rather to make substituted judgments, that is, to determine the patient's preferences. Patients' preferences are paramount; family wishes are not.

In addition, the process of making acceptable and ethical choices in such cases is difficult and emotionally draining for physicians as well as patients and families involved. The care of patients may benefit by the formation of an ethics committee to discuss those cases that possibly involve issues of withdrawing or withholding life support.

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Articles

Liver Transplantation
Experience With 100 Cases

JEAN-LUC SZPAKOWSKI, MD, *Richmand;* KEN COX, MD; PAUL NAKAZATO, MD; WALDO CONCEPCION, MD; BARRY LEVIN, MD; *and* CARLOS O. ESQUIVEL, MD, PhD, *San Francisco, California*

Between March 1988 and November 1989, 100 liver transplants were performed on 90 patients at Pacific Presbyterian (now California Pacific) Medical Center in San Francisco. The immunosuppressive regimen was a combination of prophylactic Minnesota antilymphocyte globulin, cyclosporine, and low-dose corticosteroids. Rejections were treated with OKT3, a monoclonal antibody, or corticosteroids. Of the 100 transplants, 32 were done on 30 children, 18 of whom weighed less than 10 kg and 9 of whom received livers that had been surgically reduced in size to fit the recipient. The overall patient survival at 2 years was 85%. Of 100 liver transplants, treatment was given for 80 (80%) for at least 1 episode of rejection. At least 1 episode of serious infection occurred in 34 of the 60 adult patients and 25 of the 30 children. Of the entire group, 2% had hepatic artery thrombosis, and 12% had biliary complications that necessitated reoperation. The quality of life has been good, with a follow-up from 1 to almost 3 years (mean=22 months). Comparing these data with those of other published series shows a decreased incidence of surgical complications and a lower rate of fungal and viral infections. We attribute this to the reduction of steroid dosage during convalescence without jeopardizing patient or graft survival.

(Szpakowski JL, Cox K, Nakazato P, Concepcion W, Levin B, Esquivel CO: Liver transplantation—Experience with 100 cases. West J Med 1991 Nov; 155:494-499)

Hepatic transplantation is the treatment of choice for patients with irreversible acute and chronic liver disease.[1] Although survival statistics are excellent, the procedure is still associated with substantial morbidity and mortality from surgical complications, infection, and rejection.[2-4]

The Liver Transplant Program at the California Pacific (formerly Pacific Presbyterian) Medical Center in San Francisco uses an immunosuppressive protocol combining Minnesota antilymphocyte globulin, cyclosporine, and low doses of corticosteroids in an attempt to decrease morbidity and mortality. We report, through medical records review, experience with our first 100 cases (90 patients). The procedure was done between March 1988 and November 1989, with follow-up from 12 to 34 months (mean = 22 months).

Patients and Methods

Patients who were considered to have irreversible renal failure had combined liver and kidney transplantation. Absolute contraindications for liver transplantation included seropositivity for the human immunodeficiency virus confirmed by Western blot testing or polymerase chain reaction, nonreconstructible anatomy (extensive thrombosis involving the portal, superior mesenteric, and splenic veins), extrahepatic cancer, and continued alcohol or intravenous drug abuse. Relative contraindications included congestive heart failure, severe coronary artery disease, chronic uncontrollable seizure disorder, and uncontrollable sepsis.

Organ procurement was usually performed by our transplant team using an en bloc technique.[5] All grafts were preserved with the University of Wisconsin preservation solution.[6] The recipient operation was done as described in the literature.[7] Venous bypass was used when recipients weighed more than 15 kg. Nine children received reduced-size livers[8] that consisted of eight left lobes (segments II, III, and IV), and one received a lateral segment (segments II and III). In adults, 79% of the biliary reconstructions were carried out with an end-to-end choledochocholedochostomy and 21% with an end-to-side choledochojejunostomy to a Roux-en-Y anastomosis. The latter was done in all but one child, who had an end-to-end choledochocholedochostomy. Five patients had portosystemic shunts.

Immunosuppression

The initial immunosuppressive protocol involved three drugs. Cyclosporine, 2 to 3 mg per kg per day, was given intravenously as a continuous infusion, starting on the second or third postoperative day depending on renal function. It was given orally when digestive function returned, although there was usually an overlap of intravenous and oral administration to ensure therapeutic concentrations (between 300 and 500 mg per ml). A corticosteroid regimen was begun intraoperatively with an intravenous bolus of methylprednisolone sodium succinate, 14 mg per kg of body weight, followed by a maintenance dose of 0.3 mg per kg per day given intravenously and changed to prednisone at the same dose when oral intake was begun. At the beginning of the third week, this was reduced to 0.2 mg per kg per day. Minnesota antilymphocyte globulin, a polyclonal horse γ-globulin preparation, was given for the first seven to ten days, beginning at a dose of 5 mg per kg intravenously on the first day, 10 mg per kg on the second day, and 15 mg per kg on the third and following days until therapeutic levels of cyclosporine were reached (Figure 1). OKT3 was used as induction therapy in renal failure, in patients with positive crossmatches, and in transplants across the ABO groups.

Hepatic Dysfunction

After transplantation, patients with hepatic dysfunction underwent thorough evaluations including radiologic stud-

From the Transplant Institute, California Pacific Medical Center, San Francisco, California. Dr Szpakowski is now with Kaiser Permanente, Richmond, California.
Reprint requests to Carlos O. Esquivel, MD, PhD, 2340 Clay St, #425, San Francisco, CA 94115.

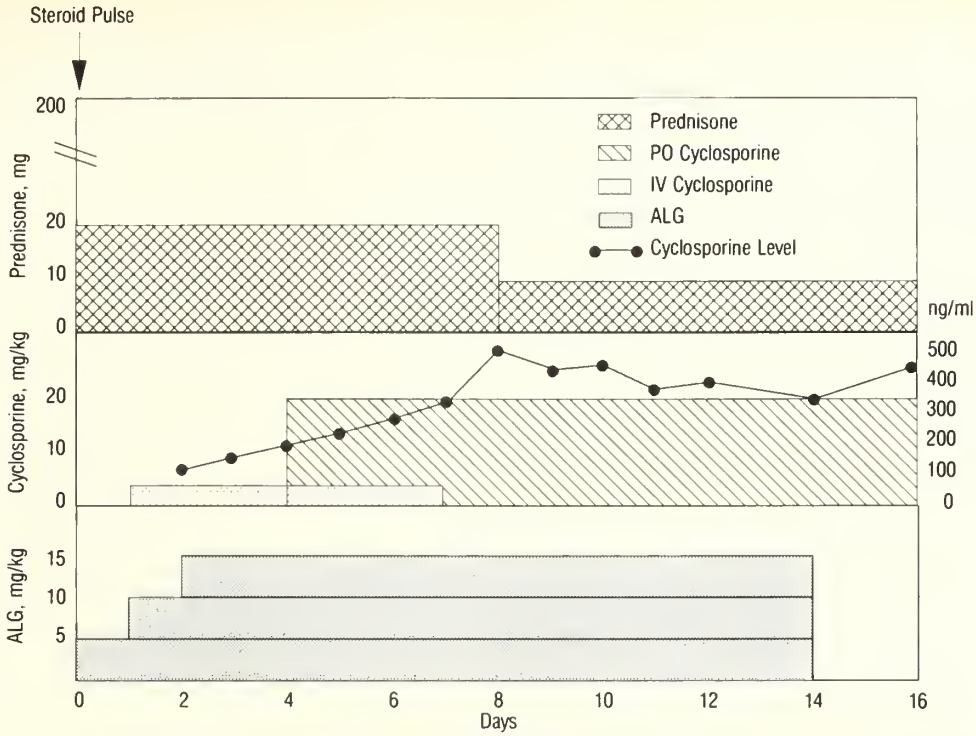

Figure 1.—The diagram shows a typical immunosuppressive regimen in a 70-kg adult following hepatic transplantation. ALG = antilymphocyte globulin, IV = intravenous, PO = oral

ies, liver biopsies, and exploratory laparotomies when necessary. Rejection, as determined histologically in most cases, was treated first with a single intravenous pulse of hydrocortisone sodium succinate, 14 mg per kg. If no response was observed, a 10- to 14-day course with OKT3 was given (5 mg per kg daily in adults and 3 mg per kg daily in children). Persistent rejection was treated with a five-day course of intravenous methylprednisolone or oral prednisone, starting with 3 mg per kg and tapering by 0.5 mg per kg per day until reaching the maintenance dose of 0.3 mg per kg per day (Figure 2). Azathioprine was not given initially to any of the patients. It was used later in some patients with persistent rejection or in others with renal dysfunction to reduce the dose of cyclosporine.

Definition of Infection and Prophylactic Regimen

A serious infection was defined as the presence of organisms cultured from tissue or fluid specimens causing clinical problems and requiring specific therapy. Minor infections did not cause clinical problems or require specific therapy. Bacterial prophylaxis included ceftriaxone sodium (50 mg per kg daily) and ampicillin (100 mg per kg daily) for 48 hours postoperatively. Most patients were treated with acyclovir (5 mg per kg daily) and immune globulin (200 mg per kg twice per week) starting in the first postoperative week and continuing throughout their hospital stay. Low doses of a combination product consisting of sulfamethoxazole and trimethoprim (4 mg per kg three times per week) or pentamidine (4 mg per kg per month intravenously or 300 mg inhaled once a month) was given for *Pneumocystis carinii* prophylaxis.

In any patient receiving prolonged broad-spectrum antimicrobial therapy preoperatively or requiring more than one laparotomy, a prophylactic regimen of amphotericin B (0.5 mg per kg daily) was begun. All children weighing less than 15 kg and those with difficult vascular reconstructions received antithrombosis prophylaxis with dextran 40 for five days plus aspirin and dipyridamole. A few patients considered to be at high risk for thrombosis also received heparin infusions postoperatively.[9]

Results

Patient Profile

Between March 1988 and November 1989, 256 patients (186 adults and 70 children) were evaluated for hepatic transplantation. During this period, 90 patients received 100 liver transplants (Table 1). Of these, 46 were male (34 adult and 12 children) and 44 were female (26 adult and 18 children). Of the 30 children, 18 weighed less than 10 kg. Two children received ABO-incompatible livers. Four adults and one child had kidney transplants during the operation or later.

The most common indications for transplantation are

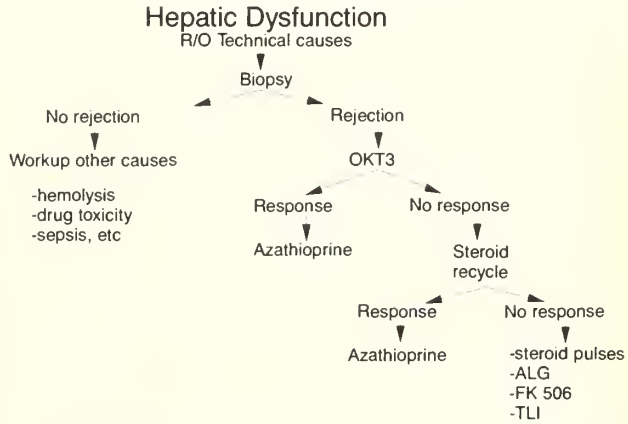

Figure 2.—This algorithm is used for the diagnosis and management of hepatic dysfunction after hepatic transplantation. ALG = antilymphocyte globulin, R/O = rule out, TLI = total lymphocyte irradiation

TABLE 1.—*Demographics of First 90 Liver Transplant Recipients*

Category	*Children (< 18 yr)*	*Adult (> 18 yr)*
Transplants, No.	32	68
Patients, No.	30	60
Mean age, yr (range)	4.1 (0.1-16)	46.48 (22-67)
Mean weight, kg (range)	13 (2-65)	68 (38-99)

listed in Table 2. Two patients underwent transplantation elsewhere and received secondary transplants at our institution. One was a child with hepatic artery thrombosis, and the other was an adult with recurrent fulminant hepatitis B. Table 3 shows the pretransplant biochemical variables of the patients according to the diagnostic indications for transplantation.

Rejection

In adults, 54 of 68 grafts (79%) had at least one episode of hepatic dysfunction treated as rejection. In children, 81%, or 26 of 32 grafts, had rejection episodes. Two patients treated with OKT3 lost their grafts from chronic rejection at 6 and 24 months after transplantation. One of these patients was an adolescent who discontinued her medications.

OKT3 was used in 28 of the 60 (47%) adults. In 10 of the patients, OKT3 was given as induction therapy and in 18 as treatment of rejection. Of 30 children, 13 (43%) were given OKT3, in 2 children as induction and in 11 as antirejection therapy. Five patients who had received OKT3 died, although only one had rejection as a contributory cause. Two died of recurrent hepatitis B, and two died of lymphoproliferative disease.

TABLE 2.—*Indications for Hepatic Transplantation*

Diagnoses	*Patients, No. (%)*
Adults (n=60)	
Cryptogenic cirrhosis	13 (22)
Laënnec's cirrhosis	11 (18)
Primary biliary cirrhosis	10 (15)
Chronic hepatitis B	6 (10)
Autoimmune hepatitis	5 (8)
Fulminant hepatitis	5 (8)
Hepatitis B 2	
Hepatitis A 2	
Drug toxicity 1	
Sclerosing cholangitis	4 (7)
Hemochromatosis	2 (3)
Wilson's disease	1 (1)
Budd-Chiari syndrome	1 (1)
α_1-Antitrypsin deficiency	1 (1)
Recurrent hepatitis (retransplant)	1 (1)
Children (n=30)	
Biliary atresia	14 (47)
Neonatal hepatitis	6 (20)
Hepatic artery thrombosis (retransplants)	2 (7)
Tyrosinemia	2 (7)
α_1-Antitrypsin deficiency	2 (7)
Autoimmune hepatitis	1 (3)
Polycystic liver	1 (3)
Drug or toxin poisoning	1 (3)
Histiocytosis X	1 (3)
Hepatoma	1 (3)
Chronic rejection (retransplant)	1 (3)

Infections

Infections in the first 90 days were documented in 64 of 100 transplants, with only 1 patient having an infection after 90 days. The number of patients treated for serious infections is listed in Table 4.

Bacterial Infections

In the 60 adults, 26 (43%) had documented bacterial infections: 15 serious infections occurred in 11 patients. Bacteremia occurred in 6 patients, acute cholangitis from intrahepatic biliary strictures in 3 patients, pneumonias in 3 patients, peritonitis in 2 patients, and 1 patient had an infected prosthetic mesocaval graft. Minor bacterial infections occurred in 15 patients.

Bacterial infections occurred in 16 of 32 transplants in children (50%). Of these, 13 patients had at least one serious episode of infection; 7 of these, however, consisted of isolated line sepsis, which was treated successfully by removing the line and administering antibiotics. The other 6 patients had a total of 9 serious infections: peritonitis (4 cases; in 2 of the 4 cases there was thrombosis of the hepatic artery), acute cholangitis from a retained stent (1 case), wound infection requiring surgical debridement (1 case), and bacteremias (3 cases). Minor infections occurred in 3 patients.

Fungal Infections

Fungal infections were uncommon. Only four adults had documented fungal infections: two had candidal peritonitis, one had candidal pneumonia, and one had aspergillar pneumonia. Six children had documented candidal sepsis: peritonitis occurred in four, wound infection in one, and catheter sepsis in one.

Viral Infections

Viral infections affected adults more often than children and were associated with more morbidity and mortality than in the children. A total of 15 viral infections were documented in 14 adult patients. Cytomegaloviral hepatitis occurred in 12 patients, 4 of whom had disseminated infection. In one other patient, influenza B pneumonitis developed within a week of transplantation, and the patient died of this infection. Viral infections were documented in six children. Viral hepatitis developed in four of the six, three caused by cytomegalovirus and one by adenovirus. All four patients recovered. In the other two children, one had respiratory syncytial virus infection and one had herpes simplex virus infection, and both survived.

Complications

Vascular complications affected three infants, all weighing less than 10 kg. These complications consisted of hepatic artery thrombosis (two infants) and portal vein thrombosis (one infant). Biliary tract complications occurred in 12 patients (9 adults and 3 children) and consisted of intrahepatic strictures from hepatic artery thromboses (2 cases), obstruction from retained stents (2 cases), bile leaks (4 cases, 2 of which occurred after T-tube removal), common bile duct stones (1), and nonischemic intrahepatic strictures (3).

Retransplantation

Of the 100 patients, 13 required retransplantation, and the indications are shown in Table 5. The retransplantation rate was 15% (9/60) in adults and 13% (4/30) in children.

TABLE 3.—*Pretransplant Biochemical Measurements* of Liver Function in Recipients According to Diagnostic Indications*

Diagnosis	*Patients, No.*	*Age, yr*	*Bilirubin, mg/dl*	*Albumin, grams/dl*	*Prothrombin Time, seconds*	*Creatinine, mg/dl*
Adults						
Cryptogenic cirrhosis	13	48.1±10	3.8±1.9	2.5±0.63	14.9±1.9	1.0±0.43
Laënnec's cirrhosis	11	48.7±11	4.8±6	2.9±0.78	15.4±2.6	1.1±0.51
Primary biliary cirrhosis	10	51±10	10.6±10	3.1±0.52	12.6±0.7	1.3±1.35
Hepatitis B	8	38±11	18.8±14.6	2.9±0.62	21.1±0.63	1.5±1.2
Autoimmune	5	40.1±15	2.2±0.9	3.0±0.42	14.1±1.87	1.0±0.51
PSC	4	47.2±14	5.9±5.5	3.1±0.61	13.0±1.4	0.9±0.14
Fulminant hepatic failure†	5	33.8±13	14.1±13.7	2.4±0.84	27±78.4	1.1±0.48
Children						
Biliary atresia	14	1.43±1.2	19.4±11	3.1±0.67	15.7±4.7	0.4±0.2
Neonatal hepatitis	6	6.7±5.4	10.6±8.7	3.1±0.47	15.2±2.2	0.6±0.7

PSC = primary sclerosing cholangitis

*Values are given as the mean and standard deviations of the mean. Conventional units are used, rather than Système International units, because these were the units used by the reporting laboratory.
†Including 2 patients with serologic test positive for anti-hepatitis B surface antibody

The survival rate in patients with retransplantations was 67%. Excluding deaths from the recurrence of hepatitis B, the one-year actuarial survival rate after retransplantation was 80%.

Patient Survival

The actuarial patient survival rate at two years for the entire series was 85% (83% in adults, 90% in children) (Figure 3). Survival was 100% in patients with Laënnec's cirrhosis, autoimmune hepatitis, and sclerosing cholangitis. It was 85% in 13 patients with cryptogenic cirrhosis and 80% in 10 with primary biliary cirrhosis. These differences between the diagnostic groups are not large enough for statistical significance (z score 18). Six of seven patients with hepatitis B became reinfected with hepatitis B within six months; three died. The other four are currently doing well with a follow-up time from 18 to 30 months. The causes of death of the 12 patients who died are listed in Table 6. Survival was somewhat less in patients older than 50 (75% of 24 patients) than in those younger than 50 (88% of 36 patients). Survival in infants weighing less than 10 kg (90%) was no different from that of larger children, nor did the survival in the cutdown livers (90%) differ significantly from that of whole organ transplantation. Two adults and one child received kidney transplants concurrently with their livers, and all had uneventful recoveries.

TABLE 4.—*Serious Infections in Liver Transplant Recipients*

Type of Infection	*Adults (n=68 transplants)* No.	(%)	*Children (n=32 transplants)* No.	(%)
Bacterial	15	(22)	13	(41)
Fungal	4	(6)	6	(19)
Viral	15	(22)	6	(19)
Total	34	(50)	25	(78)

Quality of Life

The great majority of patients have no complaints. Only three patients are unable to work because of health problems (Table 7). One has intrahepatic biliary strictures and is waiting for retransplantation. One patient has cardiomyopathy, probably due to alcoholism and selenium deficiency, and the third patient has residual central nervous system deficit from

TABLE 5.—*Indications for Liver Retransplantation*

Patient	*Age at Original Diagnosis*	*Days After Transplant, yr*	*Transplantation*	*Indication*
	Adults			
1	Fulminant hepatitis B	32	310	Recurrent hepatitis B
2	Autoimmune hepatitis	22	41	Cytomegalovirus and rejection
3	Fulminant hepatitis B	23	2	PGN
4	Postnecrotic cirrhosis	57	155	Recurrent hepatitis B
5	Fulminant hepatitis A	47	30	Epstein-Barr virus-related; lymphoproliferative
6	Cryptogenic cirrhosis	56	4	PGN
7	Fulminant hepatitis B	27	4	PGN
8	Laënnec's cirrhosis	61	0	PGN
9	Primary biliary cirrhosis	47	180	Chronic rejection
	Children			
10	Biliary atresia	0.75	3	Hepatic artery thrombosis
11	Biliary atresia	0.5	154	Chronic rejection
12	Autoimmune hepatitis	17	690	Chronic rejection
13	Biliary atresia	0.4	94	Portal vein thrombosis

PGN = primary graft nonfunction

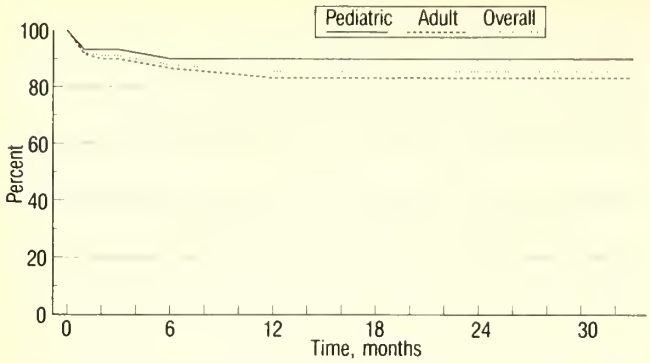

Figure 3.—The graph shows actuarial survival of 90 liver transplant recipients. Most deaths occurred within the first 6 months. Deaths after 6 months were due to the recurrence of hepatitis B. Survival was calculated using the life-table method.

Wilson's disease. Among the 11 patients with alcoholic cirrhosis, only 1 has resumed drinking. One adolescent (previously mentioned) is undergoing treatment of acute rejection after a second transplant for chronic rejection brought about by noncompliance; otherwise, the children are growing well and participating in childhood activities appropriate for their age.

Discussion

Several differences are evident when our series is compared with series published by the University of California, Los Angeles (UCLA), in 1987 and by the Mayo Clinic (Rochester, Minnesota) in 1989 (Table 8).[10,11] Patient selection criteria reflect the expanded indications for liver transplantation. Transplantation for primary biliary cirrhosis, primary sclerosing cholangitis, or autoimmune hepatitis accounted for 85% (66/78) of the adult patients at the Mayo Clinic[11] and 67% (29/43) at UCLA,[10] compared with 33% (20/60) of the adult patients in our series. The UCLA report included 1 patient with Laënnec's cirrhosis compared with 11 in our series. This latter difference dramatizes a new attitude toward transplantation for alcohol-induced liver disease, until recently a contraindication because of the fear of recidivism. Our group and others have found that recidivism has not been a problem in such patients.[12] Transplantation in patients with chronic hepatitis B is also associated with controversy,[13] but many of our patients have done well on the low-dose steroid regimen. It has not been possible to predict who will fare well with transplantation.

Our incidence of rejection is between that of the Mayo Clinic and the UCLA series. Part of this is due to the different definitions of rejection, with the Mayo Clinic requiring histologic confirmation and the UCLA series relying on clinical diagnosis.[10,11] Our approach is closer to UCLA's because we might give a single pulse of hydrocortisone without waiting for the results of a biopsy after abnormal liver chemistry values that may be early indicators of rejection. A liver biopsy is always done if OKT3 is to be used, however.[14] OKT3, which was administered to almost half of our patients, was effective in 93% of these patients. Only two failed to respond to the use of OKT3 and a second course of steroids, and both underwent successful retransplantation. No increase in morbidity occurred with the use of OKT3. The reason for using OKT3 as the initial treatment of rejection was to avoid using high doses of steroids during the period of convalescence from the operation. Steroids are well known to impair healing and to predispose to infections.[15] It has become apparent that high-dose steroid therapy is not necessary immediately after transplantation. Antilymphocyte globulin was used to protect the liver from rejection in the initial posttransplant period; its use was discontinued when cyclosporine concentrations were in the therapeutic range. With this protocol, the incidence of retransplantation for rejection was 4% compared with 11% in the UCLA and Mayo Clinic series.[10,11]

The possible consequence of an effective immunosuppressive regimen is an increased incidence of infections, for transplantation involves a balance of the two evils: infection and rejection.[16,17] The overall incidence of infections at our institution was similar to that of the Mayo Clinic[18]; the incidence of viral and particularly cytomegaloviral infection was much lower than that of the UCLA and Mayo Clinic studies, however.[10,11,18] Cytomegalovirus is a particularly important contributor to mortality in transplant patients.[19] Viral infections were the cause of death in only three of our patients and rejection in only two. Our conclusion is that our low-dose steroid regimen may have resulted in a lower rate of fatal infections, although the overall rate of infections and rejection is almost identical to that reported by other centers that

TABLE 6.—*Causes of Death in Liver Transplant Recipients (n=12)*

Patient	*Diagnosis*	*Age at Transplant, yr*	*Days After Transplantation*	*Causes of Death*
	Adults			
1	Cryptogenic cirrhosis	59	6	PGN, multiple organ system failure (MOSF)
2	Hepatitis B	60	27	Recurrent hepatitis B
3	Primary biliary cirrhosis	67	102	Rejection, CMV infection, MOSF
4	Cryptogenic cirrhosis	36	0	Intraoperative cardiac arrhythmia
5	Hepatitis B	57	90	Recurrent hepatitis B
6	Primary biliary cirrhosis	40	15	ARDS, influenza B
7	Fulminant hepatitis	47	2	PGN, MOSF
8	Hemochromatosis	59	30	Cardiac failure (cardiomyopathy)
9	Hemachromatosis	61	126	Lymphoproliferative disease, CMV infection
	Children			
10	Neonatal cirrhosis	0.1	14	Hepatic artery thrombosis, MOSF
11	Biliary atresia, fulminant hepatic failure	4.75	1	Brain-stem herniation
12	Biliary atresia	0.4	94	Intraoperative death during retransplant

ARDS = adult respiratory distress syndrome, CMV = cytomegalovirus, PGN = primary graft nonfunction

TABLE 7.—*Activity in 51 Adult Liver Transplant Recipients*

Activity	Patients No.	(%)
Employed full-time	23	(45)
Employed part-time	3	(6)
Employed but temporarily laid off	3	(6)
Unemployed, not looking for work	4	(7)
Unemployed, unable to work because of health	3	(6)
Homemaker	10	(20)
Retired	5	(10)

TABLE 8.—*Results of First 100 Liver Transplants at California Pacific Medical Center (CPMC; San Francisco),* the Mayo Clinic (Rochester, Minnesota),† and University of California, Los Angeles (UCLA)‡*

Variable	CPMC	Mayo	UCLA
Patients, No	90	83	83
Adults:children	60:30	78:5	43:40
Retransplants/patients, No.	13/13	17/16	17/13
Mean surgery time, h min	9 30	6 46	7 40
Units transfused, No.	13	18.5	17
Immunosuppression therapy			
Cyclosporine	Yes	Yes	Yes
Steroids	Yes	Yes	Yes
Azathioprine	Yes	Yes	No
OKT3, %	43	15	25
MALG, %	80§	0	0
Rejection			
Patients, No. (%)	(80)	50 (60)	83 (100)
Biopsy proven, %	67	60	NA
Infections, %	64	53	51
Hepatic artery thrombosis, %	2	10	5
Biliary tract complications, %	12	34	24
1-Yr survival, %	85	83	68
Retransplant survival, %	70	50	54

MALG = Minnesota antilymphocyte globulin, NA = not applicable

*This study.
†From Krom et al.[11]
‡From Busuttil et al.[10]
§Refers to percentage of grafts.

use conventional immunosuppressive protocols involving high-dose steroids in addition to azathioprine and cyclosporine.[4,10,11,17]

The other problem with excessive immunosuppression is an increased incidence of de novo tumors. Lymphoproliferative disease developed in 2 of 90 patients, which compares favorably with other reports in the literature.[20]

Our incidence of surgical complications was relatively low considering that a substantial number of the children weighed less than 10 kg.[21] The low rate of vascular complications may be associated with several factors. First, we routinely used aspirin and dextran 40 postoperatively along with intravenous heparin in children under 10 kg.[9] Second, the introduction of more effective solutions for preserving organs is associated with a lower rate of hepatic artery thrombosis.[22] Third, reduced-size liver transplants have the benefit of allowing anastomosis with larger-size vessels with less risk of thrombosis.[23] A final reason may be the difficulties in comparing surgical series across time. Califf and co-workers noted that survival with surgical therapy for coronary artery disease improved over the 15 years of their study period due to improvements in surgical technique and in postoperative management, including new medications.[24] Part of the same phenomenon of historical drift may be operative in comparing series of liver transplants from disparate times.

In the infants, the use of reduced-size livers has been beneficial in alleviating a donor shortage, which has led to pretransplant mortality rates in infants as high as 50%.[25] In our series, only one child (2%) died while waiting for transplantation.

Analyzing our first 100 liver transplants, we have recognized some important principles in encouraging patient survival. Early referral is critical to avoid selecting patients with end-stage liver disease and multiple organ system failure. Once it is determined that a patient is an active candidate for liver transplantation, the major factor in determining survival is the patient's overall condition at the time of the operation. Patients evaluated electively do better and at lower cost than do those referred with end-stage complications such as encephalopathy or variceal hemorrhage.[1,15] The question of the appropriateness of transplantation should at least be considered for all patients with chronic liver disease, in the same way that the question of angioplasty or bypass is considered in patients with cardiac disease.

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Articles

Recruiting Physicians to Rural Practice
Suggestions for Success

KATHERINE RILEY, PhD, *Seattle, Washington;* WAYNE MYERS, MD, *Hazard, Kentucky; and*
RONALD SCHNEEWEISS, MD, *Seattle, Washington*

Medical school graduates from 1986 to 1988 and current residents in 12 family practice residency programs in the Northwest (N=302) were surveyed to identify important factors in the recruitment process for their first postresidency placement. The study sought to compare the recruitment practices of rural communities and urban sites. Specific questions addressed in the study concerned sources of information about practice opportunities, stage in training when job search was initiated, factors related to unsuccessful site visits, and activities scheduled in the visit. Results indicated that referrals from faculty were the most valued source of information. Most job searches were initiated in the first 6 months of the third year in training. An unreceptive physician community and a reluctant spouse or partner were substantial problems for residents making site visits to rural communities. Rural sites tended to provide a broader mix of professional and personal activities during the visit.

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Physician maldistribution is a long-standing problem in this country. Assisting communities to recruit and retain health professionals is one method of addressing the situation.[1] A 1986 review of health professions redistribution programs found that 32 publicly funded programs were operating in 20 states to either assist underserved communities wishing to attract physicians or help the physicians find communities where they could establish practices.

In recent years the targets of these efforts, rural communities, have themselves taken a more active role in improving the local practice environment. As an example, several small communities in Washington, Alaska, Montana, and Idaho have participated in a community-based intervention program that seeks to improve local leadership, hospital board governance, financial management, and physician recruitment.[2] Washington in 1990 approved Senate Bill 5177, which would provide funds to rural communities to purchase technical assistance of this type for the purpose of improving local health care delivery systems.[3]

The importance of recruitment practices is further underscored by recent trends in practice choices of newly graduated residents. There is an increasing likelihood that physicians will be salaried employees. Data from a 1988 study indicate that, among physicians younger than 35 years, about 40% of all men and nearly 60% of all women are now salaried employees.[3] Additional confirmation of this development has been provided by McKinlay and Stoeckle, who concluded that young medical graduates are increasingly more interested in accepting a limited job for a guaranteed fixed income with the promise of certain attractive perquisites.[4]

Given the demonstrated interest on the part of federal and state legislators to assist rural communities to attract primary care physicians, as well as the involvement of the communities themselves, inquiry into the effectiveness of recruitment efforts of small towns is appropriate. The recruitment of physicians has been identified as a serious problem.[5] Little empiric research has been reported that describes physicians' experiences of small-town recruitment efforts. Literature concerned with physician recruitment has been based largely on professional experience[6] or general guidelines.[7] Efforts to describe the recruitment experience quantitatively have been primarily limited to identifying recruitment incentives[8,9] or considerations held to be important by health care administrators.[10]

This study was done to describe the recruitment experience of family practice residents and new graduates from training. In particular, we sought to compare the recruitment practices of small communities and urban cities. The following questions were addressed:

- Are some sources of information about practice opportunities rated more important than others?
- At what stage in their training do residents begin to identify practice opportunities?
- What factors are related to an unsuccessful site visit?
- What components are included in the site visit, and how are expenses covered?

Subjects and Methods

Subjects

Twelve family practice residency programs located in Washington, Oregon, Idaho, and North Dakota were involved in the study. These residency programs were selected for the study because their graduates represented the most likely group of prospective candidates for practice in the Northwest. Study participants were all residents who were currently in the programs as of spring 1989, as well as graduates from the previous three years, 1986, 1987, and 1988. The study was limited to these years because the researchers

From the Departments of Medical Education (Dr Riley) and Family Medicine (Dr Schneeweiss), University of Washington School of Medicine, Seattle, and the University of Kentucky Center for Rural Health, Hazard, Kentucky (Dr Myers).

Reprint requests to Katherine Riley, PhD, University of Washington School of Medicine, 1325 Fourth Ave, Suite 2000, Seattle, WA 98101.

felt practice conditions for this period had been relatively stable and the recruiting experience recent enough to be recalled with reasonable accuracy. In total, 433 physicians were eligible for inclusion in the study, 194 residents and 239 residency graduates.

Survey Instrument

A questionnaire was developed that addressed the following areas: personal characteristics and background (such as sex, age, and size of hometown); practice location preferences; job-seeking experience (sources for job leads, nature of site visits); professional and personal factors; employment profile (such as salary, benefits, and call schedule); and an open-ended section for comments. A questionnaire was also produced for the spouse or partner of the physician that included comparable sections. Both questionnaires were pilot tested with a group of family practice residents and residency graduates and their spouses or partners.

The questionnaire was mailed by certified mail to the residency graduates in March 1989. Because the marital status of the physicians was not known, a spouse or partner questionnaire was included, with the request that it be completed by the physician's spouse or partner, if appropriate. During this time, questionnaires for the residents and their spouses or partners were distributed through the residency program directors. A second questionnaire was sent three weeks later to those residents who had not responded. Analyses were conducted using the Statistical Package for the Social Sciences personal computer software ($P < .05$).

Three categories were established to define community size before data analysis. A rural community was defined as one of less than 10,000, a mid-sized town as having a population of 10,000 to 30,000, and cities as population centers having 30,000 or more inhabitants. The definition of fewer than 10,000 for rural communities was chosen because this is the working definition used by many Northwest hospital administrators and researchers involved in physician supply estimates.[11] Physicians were asked to indicate which of the three population categories best described the size of the community in which they had preferred to practice at the start of their residency and, if in practice, the population of the town they were in.

Results

The overall physician response rate was 72%; 302 questionnaires were returned of the 420 delivered. Of the 433 questionnaires mailed, 13 were undeliverable. Of the 302 respondents, 210 (69%) reported a spousal or partner relationship. Completed questionnaires were received from 156 of these persons, for a response rate of 74%. All completed questionnaires from physicians who were in nonmilitary programs or practices and who lived in the United States were included in the study. A response from a spouse or partner was included if it was complete and the physician partner had returned a questionnaire. Using these restrictions, the study yielded 273 physician and 150 spouse or partner responses. Responses were received from 95 spouses or partners of a practicing physician and 55 who were with a resident. Six spouse or partner questionnaires were not included because they were not accompanied by the physician's questionnaire.

Of the 273 respondents, 152 (55%) were physicians who were in practice, and the rest (121) were still in residency training. For the group of physicians in practice, 60 (39%) were in towns with a population of less than 10,000, 19 (12%) were in mid-sized communities, and the remaining 73 (48%) were in urban centers.

TABLE 1.—*Importance Ratings for Sources of Information on Job Opportunities**

Source of Information	Rating, Total (n=201) Mean	SD
Referrals from faculty or other physicians	3.8	1.2
Contacts you initiated through calls or visits	3.8	1.2
Contact during medical school or residency program	3.7	1.2
In-person recruitment presentation from prospective colleagues or employers	3.1	1.4
Classified ads in University of Washington's "Network News"	2.7	1.3
Referrals from family or nonphysician friends	2.6	1.3
Recruitment fairs	2.6	1.3
Direct-mail contacts	2.4	1.2
Ads in national journals	2.0	1.1
Recruitment firms	1.9	1.0

SD = standard deviation

*Ratings were done on a 5-point scale ranging from 5, "extremely important," to 1, "not important."

Sources of Information About Practice Opportunities

Ten sources of information about practice opportunities were rated on a five-point scale, with 5 being "extremely important" and 1 being "not important." Table 1 presents the importance ratings for the respondents as a whole. An analysis of variance test of each factor by the size of preferred practice community found no significant differences in mean ratings for the three community sizes for each source of information.

Initiation of Search for Future Practice

Respondents were asked to indicate when they first seriously began to identify employment options (Table 2). Third-year residents and physicians in practice indicated that the most common period for initiating a job search was the first six months of the third residency year. For the current third-year residents, 35% (18) reported that this period was the start of the search whereas 31% of those in practice (124) indicated that they became serious about identifying employment options during this summer-fall period. The least active

TABLE 2.—*Start of Job Identification by Point in Residency Training*

Reported Start Period	Job Status of Respondent: Residency, Year 1 (n=52), %	Year 2 (n=40), %	Year 3 (n=51), %	In Practice (n=124), %
Not started	63	40	--	--
Before residency	27	10	18	10
During 1st year of residency	10	5	6	6
1st half of 2nd year of residency	--	18	--	10
2nd half of 2nd year of residency	--	27	31	28
1st half of 3rd year of residency	--	--	35	31
2nd half of 3rd year of residency	--	--	10	15

TABLE 3.—*Sources of Dissatisfaction With Site Visit by Size of Preferred Practice Community**

Source of Dissatisfaction	Size of Preferred Community: < 10,000 (n=69) Mean	SD	10,000-30,000 (n=30) Mean	SD	> 30,000 (n=30) Mean	SD
There wasn't a good personality match between me and my prospective colleagues	3.7	1.4	3.4	1.3	3.3	1.5
I didn't like what I saw on the site visit	3.6	1.2	3.1	1.3	3.1	1.4
My spouse/partner wouldn't agree to make the move†	3.6	1.5	2.6	1.6	2.4	1.7
I got a better offer later	2.9	1.4	3.4	1.4	3.4	1.6
Too many practice arrangements (such as call, hours) were not thought through well enough	3.2	1.4	2.6	1.4	3.0	1.3
I didn't feel welcomed by the other physicians in town‡	3.4	1.4	2.5	1.5	2.7	1.5
Recruitment representative was too pushy and overly aggressive	3.2	1.4	2.5	1.4	2.5	1.3
Recruitment committee couldn't answer my questions acceptably	2.6	1.4	2.9	1.4	2.4	1.4
I couldn't negotiate an acceptable compensation package	2.7	1.4	2.4	1.2	2.5	1.4
Community failed to follow up on details	2.4	1.3	2.0	1.1	1.8	1.1

SD = standard deviation

*Ratings were done on a 5-point scale ranging from 5, "extremely influential," to 1, "not influential."
†$P<.001$.
‡$P<.01$

period for commencing the job search was the first year of the residency program.

Sources of Dissatisfaction With Site Visit

Ten possible causes of dissatisfaction or problems stemming from a site visit were presented for rating (Table 3). Ratings were made on a five-point scale, from 5, "extremely influential," to 1, "not influential." An analysis of variance identified two factors in which the mean values were significantly different from each other: "My spouse/partner wouldn't agree to make the move" (F_2 118 = 7.88, $P <$ .001) and "I didn't feel welcomed by the other physicians in town" (F_2 121 = 7.06, $P <$ .01). The Scheffe procedure for multiple comparisons indicated that, for both of these factors, the mean value for the rural group was significantly different from the mean values for both the mid-sized and urban communities.

As can be seen in Table 3, the failure of a good personality match with future colleagues was the most important source of dissatisfaction. This factor was ranked first by the rural group, tied for first ranking with the mid-sized community physicians, and ranked second by the urban respondents.

TABLE 4.—*Professional and Personal Components of Site Visit**

Site-Visit Components	Overall Total (n=11),* %
Professional	
Toured medical facility	84
Met hospital administrator	82
Met physicians in practice	70
Met physicians in town†	46
Worked in practice	43
Personal	
Received written information	64
Attended social event	52
Visited recreational area‡	45
Met banker or realtor‡	28
Spouse or partner received job information§	21
Received child-care information	14
Visited K-12 schools	13

*Percentage responding "Yes" that activity was included in their site visit.
†For towns with 1 or more physicians.
‡Significant difference between rural and urban communities ($P<.05$).
§For physicians with spouse or partner.

Components of the Site Visit

To assess the components of the site visit, respondents were presented with a list of five professional and seven personal events and asked to indicate whether or not they were included in their site visit schedule (Table 4). For four of the five items, rural physicians were more likely than the others to indicate that the particular component was included. The one item that urban-based physicians were more likely to have participated in was "meeting other physicians in the practice." These differences, however, failed to reach significance as measured by a χ^2 test.

Overall, the three most common site visit components were "meeting the hospital administrator," "meeting other physicians in the practice," and "touring the medical facility." Of the 47 rural-based physicians in towns with at least one other physician, 17 (36%) experienced this set of events compared with 10 (22%) of the urban group. Three urban-based physicians reported that none of these components were included in their site visits, while no rural physician experienced this situation.

By comparison with the professional aspects of the site visit, the personal factors were less likely to have taken place. As with the comparisons for the professional components, the physicians who made rural site visits more often reported that a particular event occurred during their visit than did the group visiting in urban settings.

Two components of the personal aspect of the site visit revealed significant patterns with respect to likelihood of occurrence and practice location size. Rural-based physicians were more likely than the urban group to have visited a local recreational area ($\chi^2 = 21.78$, $P < .001$). Physicians visiting small towns were also more likely than physicians in urban cities to have met with a banker or realtor ($\chi^2 = 6.13$, $P < .05$).

Respondents were also asked to indicate the source of payment (community, practice, or physician) for each of the four areas of expense incurred during the site visit: lodging, food, travel to site, and car rental. Rural communities were more likely than urban sites to have covered each of the four expenses, although no significant patterns were revealed by χ^2 analyses. The data also indicated no significant tendency for site sponsors rather than physicians to assume visit costs.

For the rural group, 29% (13) of the physicians reported that they covered all expenses, compared with 31% (10) of those in the cities. Of the rural communities hosting a site visit, 22% (10) paid all expenses compared with 10% (5) of urban hosts. The most commonly covered cost by the community sponsor for both rural and urban sites was food, with approximately 50% of physicians in both groups reporting that meal expenses were paid by the sponsor. Neither rural nor urban communities were likely to have paid for car rental costs.

Discussion

The findings of this survey point to several factors that may affect a successful recruitment effort. Importance ratings for sources of information about practice opportunities indicated a clear continuum along what could be labeled a "candid-interactive" dimension. The first preference for this group of physicians was a faculty contact, who presumably could supply a balanced picture of the potential position. The second level of preference was for personal presentations from prospective colleagues or employers. Again, the opportunity exists for substantive interaction between the two parties along with offering a personal impression. The lower importance of the rating for this source may reflect concern that a community recruiter may be less motivated to provide a well-rounded picture and more concerned about creating the most positive impression possible. Moving even farther along this interpersonal dimension was the set of sources, which included classified ads, direct-mail contacts, referrals from family and friends, and recruitment fairs. The nature of ads and mailings clearly limits the opportunity of interaction to gain more information. The low importance rating attached to referrals from friends suggests that, in addition to having the opportunity to interact, residents prefer that the source be well informed and knowledgeable about practice details. The low ratings achieved by recruitment firms and ads in national journals suggest that communities that rely on these methods may be engaging in an expensive exercise with only limited payoff.

There appears to be an optimal time during which residents direct attention toward choosing a future practice. The period encompassing the second six months of the second residency year and the first six months of the third residency year accounted for the most extensive job-search activity for both third-year residents and physicians in practice. The results of the study suggest that attempting to interest residents in future employment options during the first year of the residency program may be difficult and premature.

The two factors related to unsatisfactory site visits clearly indicate the need for rural communities to give careful attention to the details of the recruitment process. The finding that rural physicians were more likely not to feel welcomed by the other physicians in town demonstrates the importance attached to the receptivity and collegiality of the medical community by prospective physicians. The strength of this concern for good interpersonal relations was further supported by the finding that the greatest source of dissatisfaction with the site visit, regardless of community size, was the failure to experience a good interpersonal match with the physician's future colleagues.

Several explanations can be offered for these results. The failure to adequately inform other physicians in the medical community about the objectives of both the recruitment program and the planned site visit may result in local physicians being either unreceptive or unprepared to spend an adequate amount of time with visiting physicians. Contention among the medical community about current practice arrangements and how another physician may affect existing arrangements could also lead a potentially interested resident to the conclusion that the practice climate was too fractious and a better choice could be made elsewhere.

The finding that the physician's spouse or partner was less likely to agree to move to a rural community could reflect several factors. Communities may be too heavily focused on recruiting a physician and fail to realize that the spouse or partner must also be helped to appreciate why a particular practice would be a good choice. Communities may be failing to appreciate the extent to which the spouse's job is an important source of income or personal fulfillment and thus not be addressing the employment concerns of the partner.

The finding that a rural site visit tended to include a wider array of activities suggests that the recruitment trip may play a pivotal role in the resident's decision-making process. A community visit that is well organized, informative, and collegial and that adequately addresses the needs of the physician's family can be a powerful inducement to settle. A visit that presents a disinterested or contentious medical community, leaves concerns of the physician unanswered, and does not provide a meaningful schedule for the family can easily eliminate that practice from further consideration.

The purpose of this study was to describe recruitment factors and the nature of site visits. Additional research is needed to understand how much influence the site visit has when weighed against other practice considerations such as practice arrangements, client group, and location.

How can a community, particularly a rural one, be more effective in recruiting family practitioners? Several recommendations can be advanced.

- Create a recruitment committee that includes representatives with a diversity of community interests.
- Plan the recruitment strategy and methods carefully.
- Develop access to family practice residency programs and identify early those resident physicians interested in a rural practice. Stay in touch with them.
- Understand the importance of the initial impression made by the recruiter and work to develop a well-rounded and informative picture of the community and the practice.
- When preparing for a site visit, interview the physician before the visit to identify particular concerns that may not have been mentioned or apparent. Determine the aspects of the community about which the physician wants additional information. If the resident has a spouse or partner, identify that person's interests and concerns about rural living. Understand the spouse's career or homemaking plans. Ensure that the medical community has had input into the physician recruitment plan before the site visit. Endeavor to schedule uninterrupted time with other physicians for the prospective resident, apart from any planned social event. For communities that have a hospital, the visit should include an interview with the hospital administrator and other members of the practice and a tour of the community's medical facilities.
- Pay for as many of the site visit costs as possible. For recruitment committees with limited budgets, creative problem-solving to identify community assistance in the site visit could be useful.
- Call the resident after the visit to answer questions and provide further clarification, if needed.

Family practitioners are a mainstay of the health care system of many small communities. Their services are highly sought after, and the competition among rural towns for their services is intense. Rural recruitment committees could improve their likelihood of success by increasing attention to the needs of both new practitioners and the medical community at home.

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SICK CHILD

I harvest December berries
From this small child,
Whose hands are the purple of my fingers
After picking August chokecherries.

Winter aspirations from her
Clogged lungs yield
Petri dishes of microscopic fruit,
Pseudomonas aeruginosa, spreading
Their wet bathing suit bacteria smell

Across the laboratory,
Down the hall where people
Not in white wrinkle noses
And ask "what's cooking?"
As if we practice alchemy,

Conjure spells and incantations
Over work benches.
They don't know it's a miracle
This sick child needs.

STEPHANIE PERSHING BUEHLER, MT(ASCP)©
Big Horn, Wyoming

Conferences and Reviews

Molecular Mechanisms of Cancer

Moderator
H. PHILLIP KOEFFLER, MD
Discussants
FRANK McCORMICK, PhD, *and* CHRISTOPHER DENNY, MD

This is an edited summary of an Interdepartmental Conference arranged by the Department of Medicine of the UCLA School of Medicine, Los Angeles. The Director of Conferences is Anthony T. Campagnoni, PhD, Professor of Medicine.

Cancer is caused by specific DNA damage. Several common mechanisms that cause DNA damage result in specific malignant disorders: First, proto-oncogenes can be activated by translocations. For example, translocation of the c-*myc* proto-oncogene from chromosome 8 to one of the immunoglobulin loci on chromosomes 2, 14, or 22 results in Burkitt's lymphomas. Translocation of the c-*abl* proto-oncogene from chromosome 9 to the *BCR* gene located on chromosome 22 produces a hybrid BCR/ABL protein resulting in chronic myelogenous leukemia. Second, proto-oncogenes can be activated by point mutations. For example, point mutations of genes coding for guanosine triphosphate-binding proteins, such as H-, K-, or N-*ras* or G proteins , can be oncogenic as noted in a large variety of malignant neoplasms. Proteins from these mutated genes are constitutively active rather than being faithful second messengers of periodic extracellular signals. Third, mutations that inactivate a gene can result in tumors if the product of the gene normally constrains cellular proliferation. Functional loss of these "tumor suppressor genes" is found in many tumors such as colon and lung cancers. The diagnosis, classification, and treatment of cancers will be greatly enhanced by understanding their abnormalities at the molecular level.

(Koeffler HP, McCormick F, Denny C: Molecular mechanisms of cancer. West J Med 1991 Nov; 155:505-514)

H. PHILLIP KOEFFLER, MD*: Malignancy results from DNA damage that modifies the normal checks and balances that regulate cellular proliferation and differentiation. Genetic alterations that change proto-oncogenes into oncogenes activate and dysregulate normal genes and provide the cell with a growth advantage, usually in a dominant manner. Oncogenes can be created through translocations, point mutations, or amplification of genes. A loss of genetic material may also be oncogenic by the removal of a growth regulator that normally constrains cellular proliferation. Loss of these so-called tumor suppressor genes (recessive oncogenes or anti-oncogenes) is usually recessive—that is, the activity of both alleles must be missing or markedly reduced for oncogenesis to occur.

Chromosomal Structure and Neoplastic Transformation: Specific Chromosomal Abnormalities Are Linked to Certain Tumors

CHRISTOPHER DENNY, MD†: More than 95% of all tumor specimens exhibit karyotypic abnormalities[1]: duplications or deletions of genetic material or rearrangements between genetic loci on the same (inversion) or different (translocation) chromosomes. Any one tumor specimen can contain several different chromosomal abnormalities. Though many rearrangements appear to be nonspecific, specific chromosomal abnormalities are often strongly correlated with specific tumor types. In a few tumor-specific chromosomal translocations, the chromosomal rearrangements and the genetic loci adjacent to the break points have been defined at the molecular level. These rearrangements usually occur in only one allele, leaving the remaining allele karyotypically and molecularly intact, a finding consistent with a dominant effect.

Translocation could either affect the regulation of adjacent genes, resulting in structurally normal protein products being expressed at inappropriate levels, or alter coding nucleic acid sequences, creating structurally altered protein products that behave aberrantly. We examine two rearrangements, those found in Burkitt's lymphoma and in Philadelphia chromosome-positive acute lymphocytic leukemia (ALL) and chronic myelogenous leukemia (CML), to elucidate these two general mechanisms of genetic disruption brought about by genomic recombination.

Burkitt's Lymphoma—A Model for Transcriptional Deregulation

Burkitt's lymphomas contain one of three characteristic chromosomal translocations—that is, the juxtaposition of the c-*myc* proto-oncogene normally found on chromosome 8 with one of the immunoglobulin loci on chromosomes 2, 14, or 22.[2-4] The t(8;14) translocation, which occurs in 75% to 80% of patients, places immunoglobulin heavy-chain sequences upstream of c-*myc*. The variant t(8;22) and t(2;8)

*Department of Medicine, Division of Hematology/Oncology, Cedars-Sinai Medical Center, UCLA School of Medicine.

†Department of Pediatrics, Division of Hematology/Oncology, UCLA School of Medicine.

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Reprint requests to H. Phillip Koeffler, MD, Department of Medicine, Division of Hematology/Oncology, Cedars-Sinai Medical Center, UCLA School of Medicine, 8700 Beverly Blvd, Los Angeles, CA 90048.

ABBREVIATIONS USED IN TEXT

ADP = adenosine diphosphate
ALL = acute lymphocytic leukemia
cAMP = adenosine 3′:5′-cyclic phosphate
CML = chronic myelogenous leukemia
EF = elongation factor
GAP = GTPase [guanosine triphosphatase]-activating protein
GDP = guanosine diphosphate
GTP = guanosine triphosphate
PCR = polymerase chain reaction

rearrangements involve immunoglobulin λ and κ light chains and have frequencies of 15% to 20% and 5%, respectively, in Burkitt's lymphoma.

Chromosomal break points differ depending on which type of rearrangement occurs in the c-*myc* locus (Figure 1).[5,6] The major protein product of c-*myc* seems to be encoded exclusively in the last two of its three exons, although first-exon sequences may be included in a minor protein species.[7] Break points of the t(8;14) translocations occur within the first intron, the first exon, or 5′ to the c-*myc* gene (Figure 1).[8] The variant t(8;22) and t(2;8) break points are found exclusively 3′ to the last c-*myc* exon. Transcription is initiated at the normal c-*myc* promoters in exon one or at cryptic promoters in the first intron if the first exon has been deleted by the translocation. Structurally abnormal c-*myc* proteins seem not to occur in Burkitt's lymphoma.

The translocation of c-*myc* into immunoglobulin loci presumably participates in, rather than results from, tumor formation. In transgenic mice containing the Burkitt's translocation, B-cell lymphoid tumors develop at high frequency.[9,10] It is postulated that the cellular transforming effect of the Burkitt's translocation is mediated by a deregulation of c-*myc*. In Burkitt's lymphoma, c-*myc* is transcribed exclusively from the translocated locus,[11,12] suggesting that c-*myc* transcription should normally be suppressed and that, as a consequence of chromosomal rearrangement, it is not.

What is the mechanism by which c-*myc* is deregulated in Burkitt's lymphoma? Initially investigators postulated that the alteration or removal of c-*myc* first-exon sequences, which frequently occur with the translocation (Figure 1), results in the loss of important inhibitory regulatory elements.[13,14] Although regulatory elements have been identified in this region,[15] these mutations, though frequent, are not invariably present in Burkitt's tumors. Alternatively, deregulation might follow the juxtaposition of immunoglobulin enhancer elements near c-*myc*. The known enhancer elements, however, are more frequently present on the translocated allele not containing c-*myc*. Nevertheless, c-*myc* deregulation seems to be associated with the B-cell phenotype. A genomic immunoglobulin–c-*myc* construct is transcribed in a deregulated manner when placed in a Burkitt's lymphoma cell line but is normally expressed in a fibroblast cell line.[16] This suggests that c-*myc* deregulation in Burkitt's lymphoma could depend on transacting factors or higher order chromatin configurations that are B-cell specific.

Philadelphia Chromosome-Positive Leukemia—A Model of Protein Structure Alteration

The Philadelphia chromosome (Ph), the result of a characteristic translocation between band q34 of chromosome 9 and band q11.2 of chromosome 22,[17] is present in greater than 90% of patients with chronic myelogenous leukemias

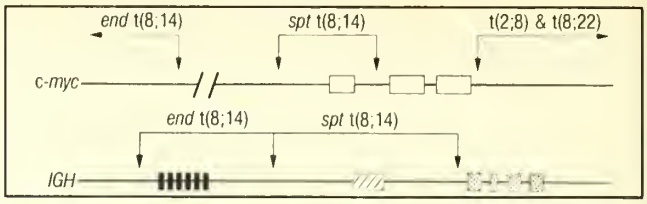

Figure 1.—The genomic representation shows the proto-oncogene c-*myc* (upper schematic) and immunoglobulin heavy chain *(IGH)* (lower schematic) translocation break-point locations in Burkitt's lymphoma. Endemic African *(end)* and spontaneous American *(spt)* Burkitt's lymphoma rearrangements can be distinguished on a molecular level by their tendencies to break at different locations in both c-*myc* and *IGH* loci (McLaughlin et al[6]). Variant Burkitt translocations occur uniformly downstream of c-*myc*. Intervening sequences are indicated by lines and exon sequences by boxes. □=c-*myc*, ■=*IGH* joining segments, ▨=*IGH* switch region, ▩=*IGH* constant segment

and 4% to 5% of pediatric patients with acute lymphoblastic leukemias.[18,19] These rearrangements in ALL and CML are karyotypically indistinguishable, but their molecular structures differ. In both instances, this translocation juxtaposes upstream regions of the *BCR* gene normally located on chromosome 22 to a distal portion of the c-*abl* proto-oncogene on chromosome 9. This results in the formation of hybrid *BCR/ABL* transcripts and proteins.

The translocation break points within the *BCR* gene have been molecularly defined. In CML, this rearrangement of the *BCR* gene (Figure 2) results in a 210-kilodalton (kd) hybrid protein (p210).[20-29] The *BCR* rearrangement in Ph-positive ALL in most cases occurs upstream of the CML break-point cluster within the 70-kilobase first intron[30-33] and produces a shorter *BCR/ABL* fusion protein of 185 kd (p185).[34-36] The messenger RNA (mRNA) coding for the p210 and p185 proteins differs only in the presence of mid-*BCR* exons. The same c-*abl* sequences are included in both molecules, which suggests that *ABL* rearrangements in Ph-positive ALL and CML are similar. A precise mapping of c-*abl* break points has been hampered by its large genomic size. The exons of c-*abl* are dispersed over at least 250 kilobases, and both ALL and CML rearrangements occur upstream of the second exon.[37,38]

The proto-oncogene c-*abl* is the normal cellular counterpart of v-*abl*, a transforming gene isolated from the Abelson murine leukemia virus. Both genes code for known tyrosine kinases, although the normal substrates that they phosphorylate are not known. The proto-oncogene v-*abl* consists of a c-*abl* complementary DNA (cDNA) that has been truncated at both 5′ and 3′ ends with viral *gag* sequences fused to the 5′ end.[39] Normal murine and human c-*abl* genes have similar

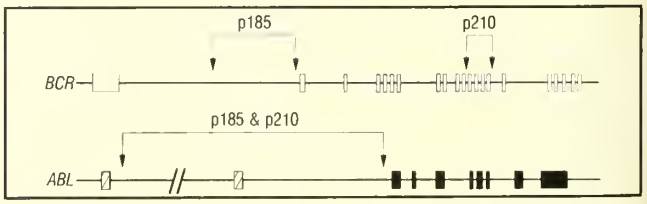

Figure 2.—The schematic shows *BCR* (upper) and c-*abl* (lower) break-point locations in Ph-positive acute lymphocytic leukemia and chronic myelogenous leukemia. Sites of *BCR* rearrangements denoted by arrows are limited to 2 regions: the distal portion of the first intron that gives rise to p185 and intron sequences of a 5-kilobase region that result in p210 formation. Recombination in c-*abl* encompasses a large, imprecisely defined region 5′ to the second exon. Schematics are not drawn to scale relative to each other. Intervening sequences are shown as lines; individual or clusters of exons are denoted as boxes. □=*BCR*, ▨=c-*abl* first exons, ■=c-*abl* common exons

genomic structures. Both use several upstream first exons to initiate transcription.[40-42] These exons account for the 26 to 45 *N*-terminal amino acids. These sequences are deleted along with the next 88 common amino acids in the *GAG/ABL* fusion of v-*abl*. The loss of these c-*abl* sequences may be important for creating the high transforming activity of v-*abl*.[43,44] In contrast to this, those regions that code for kinase domains are preserved in v-*abl* as in c-*abl*.[44,45] Ablation of kinase activity uniformly results in a total loss of transformation potential.

The *BCR/ABL* moieties may act in a similar fashion to *GAG/ABL*. As with v-*abl*, the c-*abl* first-exon sequences are lost and are replaced with varying amounts of *BCR*. Neither p185 nor p210 has the transforming capacity of v-*abl*, however. Nevertheless, retroviral constructs containing both *BCR/ABL* moieties confer a distinct growth advantage to murine long-term bone marrow cultures and clonal rodent cell lines.[46,47] Transformed clonal outgrowths are observed, but only after a more prolonged latency period than that of v-*abl*. This suggests that *BCR/ABL* alone may not suffice to transform and that subsequent events are required. In contrast to viral *GAG* sequences in v-*abl*, the incorporated *BCR* sequences may modulate the transforming activity of *BCR/ABL*.[46] Although they differ only in the amount of incorporated *BCR*, p185 has greater transformation and kinase activities than does p210. It is unclear to what extent p185 is responsible for the more aggressive clinical course of Ph-positive ALL relative to that of CML, which expresses p210.

Future Progress

Thus far, the tumor-associated translocations that have been molecularly characterized have been almost exclusively of lymphoid origin, involving either immunoglobulin or T-cell receptor genes. These loci normally undergo genomic rearrangement. This skewed population also reflects the limitations of the techniques applied to analyze these rearrangements. Only those rearrangements that involve a gene that has already been cloned are detectable at a molecular level. Most tumor-specific translocations, however, remain unexplored. Recent developments of pulse-field gel electrophoresis and yeast artificial cloning techniques permit the manipulation and isolation of large genomic fragments. These and other techniques hold considerable promise for the near future. The molecular elucidation of this wider population of rearrangements is likely to reveal other mechanisms capable of mediating cellular transformation through chromosomal recombination.

Guanosine Triphosphate-Binding Proteins as Oncogenes in Human Cancers

FRANK MCCORMICK, PhD*: The guanosine triphosphate (GTP)-binding proteins are involved in an astonishing variety of cellular processes, including signal transduction, protein synthesis, and protein secretion. At least three classes of GTP-binding proteins are known: the heterotrimeric G proteins, the *ras*-like small GTP proteins ("smg"s), and elongation or initiation factors. Proteins in each of these classes share structural similarities that are largely confined to the regions involved indirectly in guanine nucleotide binding. The nucleotide binding sites of human *ras* p21 protein and bacterial elongation factor (EF) Tu, however, are virtually identical, as determined by x-ray crystallographic analysis.[48] The structure of the GTP-binding subunit of heterotrimeric G proteins (the α-subunit) is expected to be similar to that of *ras* p21 and EF-Tu, but this has yet to be verified.

All of these proteins are regulated by guanine nucleotides; GTP-bound forms are active, whereas guanosine diphosphate (GDP)-bound forms are inactive. Hydrolysis of bound GTP to GDP occurs in all cases, although different mechanisms are used. For *ras* p21 proteins (and probably all smg proteins), hydrolysis needs other cellular proteins, referred to as guanosine triphosphatase (GTPase)-activating proteins (GAPs).[49] Elongation factors and initiation factors apparently need other proteins for this reaction. For EF-Tu, these are ribosomal proteins that ensure that EF-Tu GTP is only converted to the GDP-bound form when aminoacyl transfer RNA is correctly positioned in the ribosome. For heterotrimeric G proteins, the hydrolysis mechanism is built in, so that these proteins hydrolyze GTP at rates determined by the intrinsic properties of the protein rather than by rates determined by an interaction with other cellular molecules.

These molecular mechanisms for deactivation are a potential liability to the cell: if mutations occur that prevent the hydrolysis of bound GTP to GDP, then deactivation cannot occur and the protein from the mutated gene is constitutively active. This seems to be the method by which *ras* and G proteins become activated to become oncogenes in human cancers, as discussed later. Bacterial toxins have exploited the same Achilles heel: adenosine diphosphate (ADP)-ribosylation by cholera toxin of the G protein, known as Gs, inhibits its GTPase activity, which jams Gs in the active state. As a result, the pathway regulated by Gs (production of adenosine 3′:5′-cyclic phosphate [cAMP] by activation of adenylyl cyclase) is permanently activated.

Activation of ras *Mutations in Human Cancer*

Activated *ras* genes were the first oncogenes detected in human cancers.[50] Three *ras* genes in the human genome encode similar *ras* proteins, referred to as H-*ras*, K-*ras*, and N-*ras* p21 proteins. Mutations at codons 12, 13, and 61 occur most frequently. Originally these mutations were detected by transfecting genomic DNA from human tumors into NIH3T3 cells; foci indicated the presence of transforming genes, usually of the *ras* family. Subsequent cloning and sequence analysis, or, in some cases, altered sensitivity to restriction endonucleases showed the frequency of mutations at codons 12, 13, and 61.

The invention of the polymerase chain reaction (PCR) has made it possible to analyze many tumors for the presence of *ras* oncogenes with relatively little effort or technical expertise.[51] Briefly, DNA is isolated from biopsy tissue (which can be in the form of paraffin-embedded slices or blocks, or frozen tissue, for example), and regions of the three *ras* genes around codons 12, 13, and 61 are amplified by PCR. The PCR products are then hybridized with oligonucleotides specific for wild-type or mutant sequences. With this technique, it is possible to detect tumor cells containing point mutations in *ras* genes when the tumor DNA consists of more than about 10% of the total DNA. This imposes a limitation on the technique because it is only possible to detect mutations in cells that have undergone substantial clonal expansion. Another limitation is that mutations that are not expected (that is, not in codons 12, 13, or 61) will not be detected. Experi-

*Cetus Corporation, Emeryville, California.

TABLE 1.—*Activation of the Oncogene* ras *in Human Cancers*

Type of Cancer	*Incidence, %*	*Mutated ras Gene*
Pancreatic carcinoma	90	K-*ras*
Colon (adenoma; adenocarcinoma)	50	K-*ras*
Thyroid (follicular)	50	N-, K-, H-*ras*
Lung (adenocarcinoma)	40	K-*ras*
Acute myelogenous leukemia	30	N-*ras*
Myelodysplastic syndromes	30	N-*ras*
Kidney carcinoma, melanoma	10-20	N-*ras*
CML, ALL, CLL, non-Hodgkin's lymphoma	<5	
Breast, ovarian, cervical, bladder, stomach	<5	

ALL = acute lymphocytic leukemia, CLL = chronic lymphocytic leukemia, CML = chronic myelogenous leukemia

ence in animal and in vitro systems suggests that mutations at other positions are unlikely to occur.

Table 1 summarizes the results of some PCR analyses of *ras* mutations in human cancers. Several issues are raised by these results: first, it is not at all clear why a particular type of *ras* gene (N-*ras* versus K-*ras* and H-*ras*, for example) should predominate in a particular type of cancer. This does not seem to reflect the differential expression of a particular *ras* species in a particular type of tumor progenitor cell, as all three *ras* genes are expressed ubiquitously. The biologic properties of activated *ras* genes in vitro seem to be similar: activated K-*ras* genes are functionally interchangeable with H-*ras* genes in transforming NIH3T3 cells, for example.

The exact role of *ras* mutations in human cancers is not yet known, but *ras* activation can clearly be either an early event (possibly an initiating event) or a later event contributing to the progression to more malignant forms of the tumor. A model has been derived to explain how point mutations activate *ras* gene function (Figure 3): the active form of the *ras* p21 protein (the GTP-bound form) is converted to the inactive form by the action of a cellular protein called GAP.[49] This protein is now known to have several interesting properties beyond its ability to interact with *ras* p21: it associates with activated tyrosine kinase receptors—platelet-derived growth-factor receptor, epidermal growth factor receptor, M-central nervous system receptor—and seems to be part of the process of signal transduction from these receptors.[52] In normal cells, GAP keeps p21 in its inactive GDP-bound state through activating the GTPase of p21. In *ras*-transformed cells, however, GAP binds to the GTP-bound *ras* mutant but fails to convert it to the inactive state. This permits a persistent activation of the pathways that *ras* p21 is presumed to control, and transformation is the end result. The protein GAP itself is involved in this pathway.[49]

Heterotrimeric G Proteins

Heterotrimeric G proteins play a crucial role in transmitting signals from hormone receptors to internal second messengers. The heterotrimeric G-protein, Gs, for example, stimulates adenylyl cyclase in response to the activation of β-adrenergic receptors (Figure 3). As with *ras* proteins, the GTP-bound state of the G protein is the active state. Unlike *ras* proteins, intrinsic GTPase (rather than GAP-mediated GTPase) converts the GTP-bound state to the inactive, GDP-bound state. The exposure of cells to cholera toxin inhibits this intrinsic GTPase so that the G protein is jammed in its active state constitutively. This causes an uncontrolled accumulation of cAMP. For most cells, the overproduction of cAMP is not mitogenic. For cells of pituitary and thyroid origin, however, exposure to cAMP stimulates proliferation. This finding, together with the discovery that some pituitary tumors have high levels of cAMP constitutively, led to the speculation that these tumors contain defective G proteins that activate adenylyl cyclase constitutively and thus cause uncontrolled growth.[53] Sequence analysis of Gs-α cDNA has shown that point mutations in codons 201 and 227 occur in these tumors. Arginine 201 is a major site of ADP ribosylation by cholera toxin. Mutations at this position (like cholera toxin modification) inhibit GTPase activity. Mutations at codon 227, the Gs-α equivalent of codon 61 in *ras* p21, also inhibit Gs-α GTPase. Thus, both types of mutation resemble activating mutations in *ras* p21 and permit the G protein to exist in its active GTP-bound state constitutively.

To extend these findings, we have used PCR to examine the frequency of codon 201 and 227 mutations in 300 human tumor biopsy specimens. Of all the specimens analyzed, mutations were detected only in tumors of pituitary and (less frequently) thyroid origin.

For 16 tumors, the cyclase levels were elevated in 8 and normal in 8. All 8 high-cyclase tumors had mutations at either codon 201 or (less frequently) 227; none of the tumors with normal cyclase were found to have mutant Gs-α alleles. It thus seems that codons 201 and 227 are the most frequent sites of activation. The tumors with high cyclase levels were few, however, and it is possible that other codons are activated in Gs-α in other tumors.

We then applied the same PCR strategy to examine possible point mutations in another G protein, Gi-2, that inhibits cyclase activity (hence the name) but is also thought to be involved in other signaling pathways. It might be anticipated that mutations at equivalent positions in Gi-2 would occur in some human tumors. We therefore screened the same panel of tumors for mutations in codons 179 and 205. Of all the specimens analyzed, mutations were found only in tumors of the adrenal cortex and ovarian origin.[54] We do not yet know which pathways are turned in on these tumors to stimulate constitutive growth; clearly this is of great interest to the understanding of the development of these kinds of cancer.

Summary

Mutations of the *ras* and heterotrimeric G proteins can persistently activate the pathways that these proteins control. In some cases, these pathways seem to be involved in the control of cell growth, and their achromic activation is thought to cause uncontrolled cell division. This seems to be a major mechanism for the development of tumors in humans and will be the focus of attempts in the future to improve diagnostic and therapeutic methods.

Tumor Suppressor Genes

DR KOEFFLER *and* CARL W. MILLER, PhD*:

Somatic Cell Hybrids

Original evidence for tumor suppressor genes was indirect. The fusion of a normal and a tumor cell results in somatic hybrids that usually have the phenotype of the normal cell and are nontumorigenic.[55-59] These somatic hybrids lose chromosomes, and, with this loss, the hybrids occasionally revert to a tumorigenic phenotype. This reversion per-

*Department of Medicine, Division of Hematology/Oncology, Cedars-Sinai Medical Center, UCLA School of Medicine.

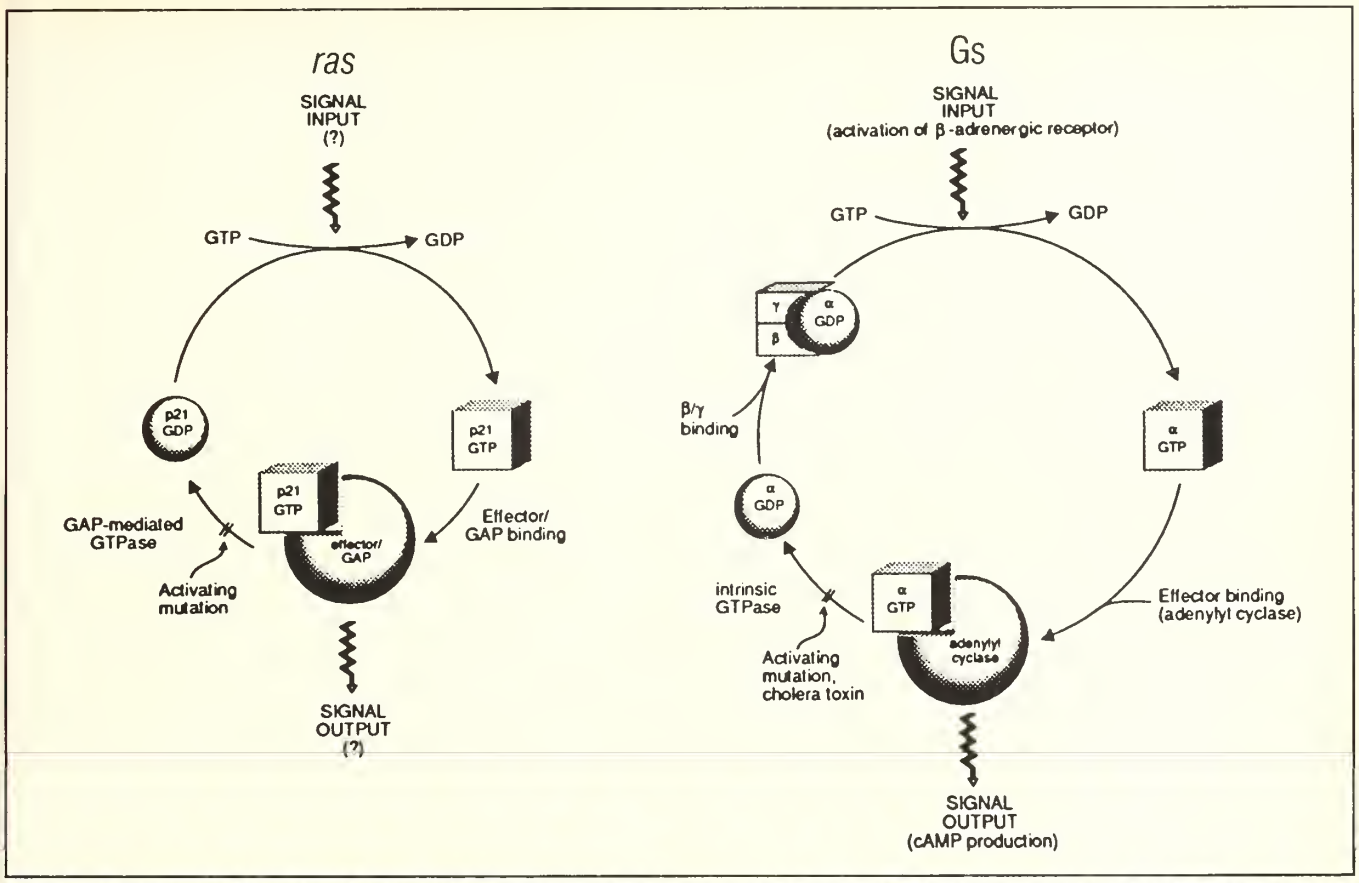

Figure 3.—The regulation of *ras* p21 and Gs proteins by the guanine nucleotides guanosine diphosphate (GDP) and guanosine triphosphate (GTP) is schematically depicted. GAP=guanosine triphosphatase (GTPase)-activating protein

mitted the identification of chromosomes associated with the normal phenotype, which, when lost, resulted in a return to the malignant phenotype. This technique has become more sophisticated: single normal chromosomes added to malignant cells permit the identification of normal chromosomes, which can cause a reversion of specific malignant cells to a nonmalignant phenotype (Figure 4). For example, the insertion of normal chromosome 11 can cause cells from cervical carcinomas, Wilms' tumors, and rhabdomyosarcomas to revert towards a normal phenotype.

Karyotypic Analysis

Specific chromosomal deletions are associated with malignant tumors. Leukemia cells, because of their availability and ease of growth in liquid culture, provided one of the earliest paradigms that specific subtypes of leukemia were associated with specific, nonrandom losses of chromosomal material. For example, a loss of the long arm of chromosome 5 (5q) or 7 (7q) is found in a recognizable group of patients with either preleukemia or acute myelogenous leukemia, who previously had exposure to a mutagen such as alkylating chemotherapy. Karyotypes of solid tumors have also identified nonrandom losses of chromosomal material. Chromosomal deletions at 3p, 11p13, 13q14, and 22 frequently occur in patients with lung cancer, Wilms' tumor, retinoblastoma, and acoustic neuroma, respectively.

Loss of Heterozygosity

The use of restriction-fragment-length polymorphism to identify allelic loss is a powerful method to associate specific tumors with specific chromosomal deletions. These deleted areas often represent regions where a normal allele has been lost and a mutated allele has been duplicated by either nondisjunction or mitotic recombination. Thus, a reduction to homozygosity unmasks the recessive, defective allele. A loss of heterozygosity of various chromosomal regions is the tombstone that identifies genes whose homozygous functional loss triggers tumor formation. Many probes are now available to identify restriction-fragment-length polymorphisms. Probes that identify varying numbers of tandem repeats of DNA sequences are particularly useful because each can distinguish corresponding parental alleles in a high proportion of normal DNA specimens.[60] Table 2 provides a partial list of chromosomal locations that are associated with a loss of heterozygosity in human tumors.[61-82]

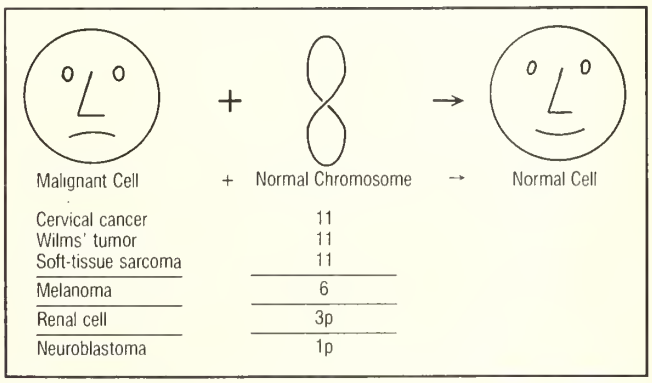

Figure 4.—Examples are shown of specific normal chromosomes that, when placed into a cell, can cause a malignant cell (symbolized by a frowning face) to revert to a nonmalignant cell (symbolized by a smiling face).

TABLE 2.—*Loss of Heterozygosity in Human Tumors*

Chromosome	Type of Cancer	Reference
1p	Breast; melanoma; neuroblastoma; pheochromocytoma	Limon et al, 1988[61]; Genuardi et al, 1989[62]; Tsutsumi et al, 1989[63]
1q	Breast	Chen et al, 1989[64]
3p	Lung; cervical; renal	Naylor et al, 1987[65]; Yokota et al, 1987[66]; Kovacs et al, 1988[67]; Yokota et al, 1989[68]
5q	Colon, myelodysplastic syndrome	Solomon et al, 1987[69]; Vogelstein et al, 1989[70]; Nagarajan et al, 1990[71]
11p	Breast; lung; bladder; Wilms' tumor; hepatoblastoma	Fisher et al, 1987[72]; Mackay et al, 1988[73]; Weston et al, 1989[74]; Mannens et al, 1990[75]; Tsai et al, 1990[76]
11q	MEN-1	Larsson et al, 1988[77]
13q	Lung; stomach; retinoblastoma; osteosarcoma	Yokota et al, 1987[66]; Motomura et al, 1988[78]
17p	Breast; lung; colon; cervical; bladder; ovary; osteosarcoma	Yokota et al, 1987[66]; Weston et al, 1989[74]; Tsai et al, 1990[76]; Monpezat et al, 1988[79]
18q	Colon	Monpezat et al, 1988[79]
22	Meningioma; acoustic neuroma; pheochromocytoma	Rouleau et al, 1987[80]; Takai et al, 1987[81]; Okazaki et al, 1988[82]

MEN-1 = multiple endocrine neoplasia type 1

DNA-Transforming Viruses

Proteins coded by DNA-transforming viruses often bind to cellular proteins. The simian virus 40 (SV40) T antigen, adenovirus E1A, protein E7 of human papillomavirus type 16, and polyoma T antigen can bind and possibly inactivate Rb protein, a putative tumor suppressor protein missing in retinoblastomas. Furthermore, SV40 T antigen, adenovirus E1B, and protein E6 of human papillomavirus type 16 can bind and perhaps inactivate the p53 protein, also a putative tumor suppressor. The viral oncoproteins may trigger abnormal proliferation by blocking key regulatory functions of Rb and p53, which are normally responsible for constraining cellular proliferation.

Other as-yet-undefined cellular proteins also bind to DNA-transforming viruses. DNA-transforming viruses may be our fishing nets to catch and identify new tumor suppressor proteins.

Tumor Suppressor Genes

Five tumor suppressor genes have been cloned: *RB* ("retinoblastoma susceptibility" gene),[83] *P53*, *DCC* (deleted colon cancer "gene"),[84] *MCC* (mutated colon cancer gene),[85] and *WT* (Wilms' tumor gene).[86,87]

RB. The *RB* gene, located at chromosome 13, band q14, codes for a protein that does not change in amount during the cell cycle.[88,89] The Rb protein is a 110-kd unphosphorylated nuclear protein during G_0 and G_1 stages of the cell cycle and a phosphorylated 115-kd protein during S and G_2.[90,91] Terminally differentiated normal cells, such as macrophages, have a predominance of phosphorylated Rb. The transforming protein (T antigen) of SV40 binds only the unphosphorylated form of Rb, which may constrain cell cycle progression. Release of this constraint may be by phosphorylation of Rb in normal cells after exposure to growth factors or by either mutation of *RB* or the binding of viral protein (for example, T antigen) to Rb, which releases critical constraints in the cellular regulatory circuitry. Cloning of the *RB* gene has permitted molecular genetic analysis of retinoblastoma and other malignant neoplasms that have a loss of heterozygosity of restriction-fragment-length-polymorphism at 13q14. Transfection of the *RB* gene into tumor cell lines bearing *RB* gene abnormalities inhibits proliferation.[92] Rearrangements of the *RB* gene have been found in retinoblastomas, osteosarcomas, lung cancers, and leukemias.

P53. The *P53* gene, first identified in the nucleus of 3T3 murine cells transformed by SV40,[93] binds heat-shock protein, a protein (which may be cdc-2), and single-stranded DNA.[94-96] It competes with DNA polymerase-α for binding to T antigen, suggesting *P53* may be involved in the regulation of the cell cycle. We and others have shown that *P53* can act as a transcriptional activator, presumably activating genes that regulate cell proliferation.[97-99]

Several observations define *P53* as a tumor suppressor: transfection of normal *P53* into rodent cells decreases the transformation potential of activated *ras* plus either *myc*, mutant *P53*, adenovirus E1A, or SV40 T antigen.[100] In addition, transfection of normal *P53* gene into cell lines bearing mutant or rearranged *P53* inhibits proliferation of the cells.[101,102] Mutant *P53*, on the other hand, has the ability to confer transformed phenotype on rodent primary cells in culture.[103,104] Transgenic mice carrying a highly expressed mutant *P53* have an increased incidence of several cancers.[105] Mutant *P53* in these mice may compete with normal *P53* to prevent normal suppressive interaction of *P53* with either DNA or other proteins. A loss of heterozygosity of chromosome 17p is a feature of many cancers, occurring in at least 60% of the tumors of colon, breast, lung, brain, cervix, adrenal cortex, bone (osteosarcoma), and urinary bladder. About 20% of human osteosarcomas have gross rearrangements of the *P53* gene detectable by Southern blots.[106,107] Mutations of *P53* have been detected in cancers of colon, lung, and esophagus, T-cell leukemias, chronic myelogenous leukemias, brain and breast cancers, and a variety of cell lines.[104,108] Most of these mutations occurred in four "hot spots" that represent evolutionarily conserved regions of *P53*.[109] Cellular transformation by viruses may be mediated in part by viral antigen binding of *P53*. For example, *P53* binds to SV40 T antigen and adenovirus E1B, perhaps contributing to transformation by interfering with the tumor suppressor function of *P53*.[93,110] This interaction may cause transformation by inactivating the tumor suppressor activity of *P53*. Many similarities exist between *P53* and *RB*: both bind to T antigen of SV40.[93,111] *RB* binds to E1A, and *P53* binds to E1B of adenovirus.[110,112] These viral proteins may foster tumor formation by binding and inactivating the suppressor function of *RB* and *P53*.[107,108]

DCC. The *DCC* (deleted colon cancer) gene on the long arm of chromosome 18 is frequently abnormal in colon cancer.[62] The predicted amino acid sequence of *DCC* is highly similar to a neural cell adhesion molecule. Expression of this gene is greatly reduced or absent in colorectal cancers. Most

frequently, this gene is disrupted in colorectal tumors by DNA insertions in one of its introns. Perhaps *DCC* protein plays a role in the pathogenesis of colon cancer by altering the normal cell-cell interactions controlling growth.

WT. A loss of heterozygosity affecting the short arm of chromosome 11 occurs in Wilms' tumors. The putative tumor suppressor gene involved at this locus is known as the *WT* gene.[86,87] The *WT* product has properties of a transcriptional activator and has DNA binding specificity for the epidermal growth factor I gene.[113] Deletions and rearrangements of the *WT* locus have been reported in Wilms' tumors.[114,115]

MCC. Allelotype analysis of colorectal cancer frequently shows a loss of heterozygosity affecting the long arm of chromosome 5. A gene frequently mutated in this region in colorectal cancer has been identified and named a mutant in colon cancer *(MCC)*. This gene has sequences suggesting that it is related to the G-protein family.[85]

Tumors

Retinoblastoma. Retinoblastoma is a malignant neoplasm of the retina that occurs in children usually younger than 4 years. It occurs in hereditary and nonhereditary forms. About 40% of patients with retinoblastoma have the hereditary disease; therefore, the predisposition of retinoblastoma is passed to their progeny as an autosomal disorder. Only 25% of these patients with retinoblastoma have a familial history of the disease; new *RB* mutations of the germ cells probably occur in the remaining 75% of those with familial retinoblastoma. These germ-line mutations of *RB* almost always occur on the paternal allele.[116]

In patients with hereditary retinoblastoma as compared with the nonhereditary form, tumors usually develop at an earlier age and are more frequently multifocal. Tumor formation requires that both *RB* alleles be either altered or inactivated. In the hereditary form, one *RB* allele is already mutated in the germ line. In the nonhereditary or "sporadic" form, two rare somatic alterations are needed within the same retinal precursor cell to eliminate the expression of normal *RB*. Several mechanisms might account for the loss of a second, normal *RB* gene. A random somatic mutation, such as a point mutation, could occur on the second allele. The frequency of this second mutation is low, about 10^{-6} per cell generation. More frequent genetic events are either mitotic recombination or gene conversion of the entire region of the chromosome carrying the mutated *RB*. This produces a doubling of the initially defective allele and loss of the hitherto normal chromosome. This reduction to homozygosity, which unmasks a recessive, defective allele, may be a frequent genetic mechanism by which other genes behave like the *RB* gene in tumorigenesis. About 20% of retinoblastomas have either a large deletion or rearrangement of the *RB* gene; most of the others have point mutations. Most frequently a point mutation of these produces a stop codon, halting translation of the *Rb* protein. Mutations at mRNA splice sites also occur often, and missense mutations occur occasionally. Most retinoblastomas do not express *Rb* protein.

Patients with hereditary retinoblastoma have an increased incidence of osteosarcomas, suggesting that a loss of the expression of *RB* is important in that tumor also. Most osteosarcomas develop after the patient has a retinoblastoma, suggesting that the former malignant tumors need mutations in addition to *RB*. Somewhat perplexing is the infrequency of reports of urinary bladder, breast, or lung cancer in patients with hereditary retinoblastomas. Each of these tumors is associated with a mutated *RB* gene. Perhaps these cancers need the accumulation of so many mutations that heterozygosity for an *RB* mutation does not provide a great liability.

Lung cancer. Tobacco smoke is the major causal agent that contains numerous chemical and physical carcinogens and clastogenic agents. These play an interactive role in the genetic changes that occur during the multistage process of carcinogenesis of lung. One or several proto-oncogenes may be activated in these tumors, including members of the *myc*, *ras*, *raf*, and *jun* multigene families.[117] The inactivation of several tumor-suppressor genes is probably also important.

The most frequent cytogenetic abnormality in lung cancer is deletion of the chromosomal region 3p14–23. Cytogenetic abnormalities in this region occur in about 70% of small-cell and 60% of non–small-cell lung cancers.[65,66,118] Analysis of restriction-fragment-length polymorphism shows a frequent loss of heterozygosity of several other chromosomal regions, suggesting that lung cancers result from the accumulation of mutations of several oncogenes.[66,70,74] The loss of heterozygosity of specific chromosomal regions varies between different histologic subtypes.[74] For example, a loss of heterozygosity on 3p and 13q (*RB* gene) occurs more frequently in small-cell lung cancer than in non–small-cell lung cancer.[66,74] More than 75% of squamous cell cancers have a loss of heterozygosity for 17p (*P53* gene); in contrast, less than 20% of adenocarcinomas have a loss of heterozygosity for this region.[66,74] A loss of heterozygosity for 3p, 13q, and two loci on chromosome 11 (11pter–p15.5; 11p13) are of equal frequency in both squamous cell carcinoma and adenocarcinoma of the lung.[74] The risk of squamous cell lung cancer is greater in heavy smokers (>1 pack per day) than is the risk of adenocarcinoma. Taken together, this suggests that an inactivation of *P53* (17p) may be closely associated with the smoking of cigarettes and the development of cancer.

Major rearrangements of the *RB* gene occur in about a sixth of small-cell lung cancers,[119] but the methods used are insensitive for detecting point mutations. Expression of Rb mRNA was absent or barely detectable in cell lines from 75% of small-cell lung cancers and 20% of non–small-cell lung cancers. The Rb protein may be absent in nearly all small-cell lung cancers and 20% of non–small-cell lung cancers.[110] Analysis of *P53* in cell lines from 14 small-cell and 15 non–small-cell lung cancers showed that more than half of the specimens had DNA abnormalities including point mutations.[66] Our analysis of 40 lung cancers with a loss of heterozygosity of chromosome 17p showed a 30% frequency of *P53* mutations in these specimens.

Colon cancer. Allelotyping of allelic deletions using probes for every relevant autosomal arm suggests that colon cancer probably develops as a result of a multistep process of mutagenesis (Figure 5).[70] Deletion on chromosome 5q (35% incidence) and mutations of K-*ras* (45% incidence) usually occur at a relatively early stage of tumorigenesis. Allelic deletions of chromosomes 17 (region of *P53*), 18 (region of *DCC*), and 5 (region of *MCC*) often develop at a later stage of carcinogenesis. The order of these changes, however, is probably less important than their accumulation. Alterations probably continue to accumulate even after colon carcinoma

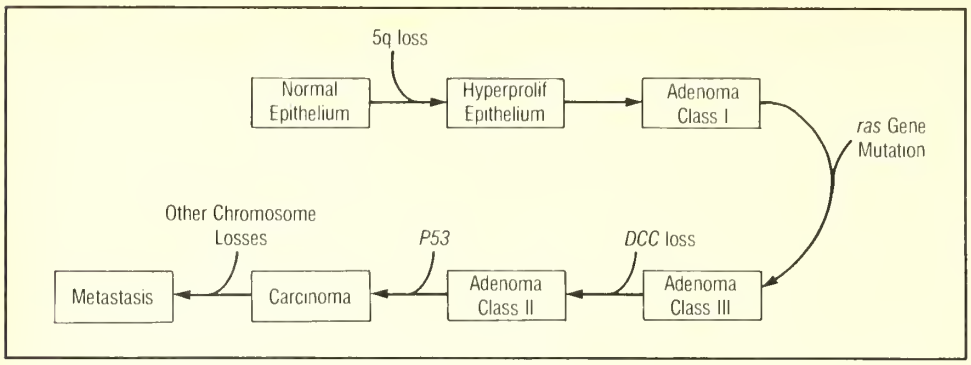

Figure 5.—The diagram shows the accumulation of mutations that can cause a normal colonic cell to become an adenocarcinoma cell. The tumor suppressor gene on the long arm of human chromosome 5 (5q) is *MCC* (Kinzler et al[85]). The drawing is adapted from studies by Vogelstein et al.[70]

develops. Most colon cancers have from three to six genetic alterations. Patients with greater than 20% allelic losses have a poor prognosis and are more likely to get a recurrence of their disease and to die of colon cancer.[121] Most of the allelic deletions are subchromosomal, rather than a loss of an entire chromosome.[121]

The *DCC* protein is not expressed in colon cancer, whereas it is expressed in most normal tissues. The *P53* gene is often mutated in colon cancer, and most of these are missense mutations.[108] More than 75% of colon tumors express apparently normal-sized *P53* mRNA, but little is known of the expression of p53 protein in these specimens.[108] A loss at 5q15–q22 seems to be specific to colorectal tumors, and the relevant gene in this region may be the *MCC* gene, which has some homologies to a G-binding protein. Patients with hereditary adenomatous polyposes coli *(APC)* have deletional mutation in this region, but the other allele seems to be normal, suggesting that a mutation of only one allele is sufficient for adenoma formation. This mutated gene, therefore, is not acting recessively. An array of linked DNA probes flanking the *APC* gene now permits the identification of persons who have inherited a mutated *APC* and have at least a 50% chance of carcinomas developing. These patients need close monitoring and prophylactic colectomy.

Urinary bladder cancer. Patients with bladder cancers often (70%) have a loss of heterozygosity of 17p (location of *P53*), 9q, and 11p. Deletions on 6p (30%) and 14q (20%) occur less frequently.[76,122] A coincidental loss of 17p and 11p in bladder cancers (50% incidence) is similar to findings in squamous cell carcinoma of the lung.[74,76] Cigarette smokers have an increased incidence of urinary bladder cancer; perhaps cigarette smoke preferentially causes mutations in genes in these regions.

Astrocytomas. Gliomas are the most common primary tumors of the human central nervous system, most of which are astrocytomas. A loss of heterozygosity of chromosomal regions in astrocytomas occurs on chromosomes 13, 17, and 22, with nearly 50% of the tumors having a loss of 17p.[123] A loss of heterozygosity on 17p occurs in high- and low-grade astrocytomas, suggesting that abnormalities of *P53* occur at an early stage of tumor formation. Patients with the Turcot syndrome have familial polyposis and either malignant astrocytoma or medulloblastoma. This is consistent with a mutated *P53* being associated with tumorigenesis of colon cancer and astrocytomas. Perhaps these patients have hereditary mutation of *P53*, as has been described in the Li-Fraumeni syndrome. In families with the Li-Fraumeni syndrome, one *P53* allele has a mutant codon between residues 240 and 260. Diverse mesenchymal and epithelial neoplasms develop at multiple sites in these patients.[124,125]

Suppressor Genes and the Heterozygous State

Tumor suppressor genes are thought to act in a recessive manner.[56,126] That is, inactivation of both parental alleles is needed if a loss of the constraining effects of a normal tumor suppressor gene is to occur. The paradigm for this concept is retinoblastoma. Recessive action may not always be the case in other cancers, however. Hereditary tumors of some patients have not lost the normal allele that corresponds to the mutated locus linked to the predisposition to cancer, such as neurofibromatosis type 1, multiple endocrine neoplasia type 2, and adenomatous polyposis coli. Here the normal alleles of chromosomes 17, 10, and 5, respectively, seem to be intact in the familial tumors.[127] Also, transfection of a mutated *P53* gene into normal fibroblasts can cause transformation; this occurs even though these cells also express normal *P53*.[128,129] The *P53* produces oligomers, and perhaps the oligomerization of normal and mutated *P53* alters the function of the normal *P53*, explaining the dominant effect of such a *P53* mutation. In brief, mutations of some tumor suppressor genes may affect growth even in the presence of a normal allele.

Future Direction

In the coming decade, we should see a rapid advancement in the clinical application of the evolving knowledge of tumor suppressor genes. We should be able to use the polymerase chain reaction to identify rapidly the loss of tumor suppressor genes by analyzing a variable number of tandem repeats using only a few tumor cells. The classification and prognosis of these cancers will be possible by rapidly identifying all mutations of tumor suppressor genes in the patients' tumor cells by analyzing the loss of heterozygosity. A targeted replacement of deleted or mutated tumor suppressor genes in either the tumor or premalignant tissue may permit a reversal of malignancy in these patients.

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Epitomes

Important Advances in Clinical Medicine

Psychiatry

The Scientific Board of the California Medical Association presents the following inventory of items of progress in psychiatry. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome, and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, researchers, or scholars to stay abreast of these items of progress in psychiatry that have recently achieved a substantial degree of authoritative acceptance, whether in their own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Psychiatry of the California Medical Association, and the summaries were prepared under its direction.

Reprint requests to Division of Scientific and Educational Activities,
California Medical Association, PO Box 7690, San Francisco, CA 94120-7690

Electroconvulsive Therapy

THERE IS A PERSISTENT ANTIPATHY to the use of electroconvulsive therapy (ECT), despite repeated evidence of its efficacy and safety. In response to public demands, the National Institutes of Health held a consensus conference in 1985. The conferees endorsed the efficacy of ECT in a number of conditions, noted its safety when properly done, and asked for the development of guidelines to treatment as the basis for its broader use. In response, the American Psychiatric Association established its second Task Force on Electroconvulsive Treatment, the report of which was published in May 1990. The recommendations summarize the present standard of care and its rationale and include a bibliography of sources.

The safety and efficacy of ECT in treating patients who have major depressive disorders, with melancholia or psychosis, make these diagnoses the main indications for its use. Its effectiveness in patients with manic delirium; with acute schizophrenia with symptoms of hallucinations, delusions, and paranoia; schizoaffective disorders; and catatonia is now recognized.

The report describes situations in which ECT may be the first treatment: when a rapid definitive response is required for medical or psychiatric reasons, when the risks of other treatments outweigh those of ECT, when there is a history of poor drug response or of good ECT response in previous episodes, and when a patient prefers it. Conditions that may require a rapid response include manic delirium, catatonic excitement, suicidality, inanition, or severe motor inhibition (catatonia). A common use is in patients admitted to hospital with affective and psychiatric disorders in whom other therapies failed or who were unable to tolerate other treatments because of side effects.

There are no absolute contraindications to using ECT, but conditions of substantial risk may require special skills. The presence of increased intracranial pressure, unstable cardiovascular function, aneurysm, or conditions that are rated as anesthetic risks—American Society of Anesthesiologists level 4 or 5—are examples. Much of the skill in treating high-risk medically ill patients lies in the treatment "team," consisting of a psychiatrist, an ECT nurse, and an anesthetist.

Consent is an important consideration, and the task force urges the signing of a specific consent document that outlines the reasons for the treatment, alternative remedies, a description of the treatment, the number and frequency of treatments, and the caveat that the patient may end the course at any time. Modern ECT is "modified," in which treatments are given under anesthesia with ventilation and oxygenation, with special attention to electrode placement, brief-pulse currents, and low doses of energy. Under these conditions, the side effects described in the earlier literature—panic, delirium, fracture, organic psychosis, and cognitive deficits—no longer occur.

Present ECT practice is described in sufficient detail to provide standards for care. The early training of practitioners in ECT remains a function of medical school and residency training programs. To supplement these, the report encourages continuing medical education courses. In the past year, these have been developed at the Chicago Medical School (North Chicago, Illinois), Duke University (Durham, North Carolina), State University of New York at Stony Brook, Washington University (Saint Louis, Missouri), and CME, Inc (Tustin, California). Because ECT is generally given in a hospital or other medical facility, the granting of ECT privileges is the responsibility of the medical director or medical board of each institution, and each organization is encouraged to develop guidelines for granting privileges.

Electroconvulsive therapy remains "controversial" because of professional and lay misperceptions. It is a tragedy that the principal beneficiaries of the treatment, those who require admission to hospital, are denied the treatment by its unavailability in most state, federal, and municipal psychiatric hospitals—precisely the places where most of the candidates with the best indications and prognosis are treated. The present American Psychiatric Association's Task Force report is a rational, detailed, and thoughtful document that should be the basis for improved training in medical schools and residencies and for the establishment of ECT treatment teams at psychiatric and medical centers.

MAX FINK, MD
Stony Brook, New York

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Electrophysiologic Evaluation for Brain Dysfunction

In addition to passive electroencephalography, activated brain electrical responses to sensory stimulation and cognition can now be recorded. Responses emerge as stimulus or as event-related evoked-potential small microvolt patterns buried in larger microvolt electroencephalographic patterns. To extract evoked-potential patterns, stimulation is presented repeatedly and responses averaged. Background electrical "noise" essentially cancels out, and unique brain patterns can be elicited and analyzed. Different patterns are obtained for different sensory modalities, different neuropsychological tasks, and different physical and psychiatric conditions. Auditory and somatosensory stimulation provides information on brain-stem, subcortical, and cortical responsivity. Visual stimulation provides information on retinal responsivity, transmission through visual pathways, and cortical responsivity.

Electrical potentials have known latencies and central conduction times between different central nervous system relay stations. In the auditory system, for example, certain brain-stem delays can indicate an acoustic neuroma or the effects of alcoholism. Important qualitative data can be obtained. In comatose or near-comatose victims, it is possible to evaluate the functioning not only of the ears and eyes, but of the upper and lower extremities and the spinal cord with respect to ability to transmit afferent somatosensory information. It is also possible to assess the extent and degree of abnormality of cortical responses in different regions of the brain.

Multisensory evoked-potential patterns can be read reliably and yield evoked-potential scores indicating an abnormality. Such scores are correlated significantly with cortical dysfunction, cognitive and behavioral clinical impairments, and, to a lesser degree, with prognosis after severe brain injury. Evoked potentials can be used as a tool in neuropsychiatric assessment to help differentiate organic from functional disorders. Mapping brain electrical activity topographically and comparing the results statistically with normative data is another method of assessing central nervous system dysfunction associated with physical, psychiatric, and psychophysical conditions.

A case of suspected conversion disorder involving reportedly sudden hearing loss was shown definitely by evoked-potential testing to be a neurophysiologic and not a psychological problem. Another case involving an industrial injury in which a blow to the side of the head was reported to have caused a peripheral hearing impairment was shown to be an incident of malingering. Another case of psychological blocking and cognitive impairment thought initially to be caused by psychological trauma was shown by electrophysiologic finding to be more closely associated with a dysfunctional brain disorder compatible with an organic brain syndrome.

MAURICE RAPPAPORT, MD
San Jose, California

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Prophylaxis of Antipsychotic Drug-Induced Extrapyramidal Syndromes

In the past, the psychiatric literature contained a virtual prohibition against the use of anticholinergic drugs before the onset of neuroleptic-induced extrapyramidal syndromes. Some controversy continues today regarding the risks and benefits of the prophylactic use of anticholinergics. Recent studies indicate, however, that this use of anticholinergic drugs and perhaps other drugs to counteract extrapyramidal syndromes should be considered for some patients. Several reasons are given for prophylaxis: First, these syndromes cause pain, discomfort, and incoordination. Laryngeal or pharyngeal dystonia may jeopardize life. Patients may refuse to take antipsychotic drugs or leave the hospital before the completion of treatment when experiencing these side effects. Preventing the neurologic side effects of antipsychotic drugs helps reduce morbidity and ensure patient compliance. Second, some side effects can exacerbate or mimic the symptoms of schizophrenia, leading to inappropriate treatment. Akathisia, for example, can cause patients to appear to be more psychotic. Left untreated, drug-induced parkinsonism and akathisia can make a normal social life and adequate job performance impossible, defeating efforts at psychosocial rehabilitation.

The benefits of prophylaxis for extrapyramidal syndromes must be weighed against the risks. Anticholinergic and other medications to treat these disorders are not benign; undesirable effects include blurred vision, dry mouth, and constipation. Impairment in short-term memory may be common even with therapeutic doses. In rare cases, complications as severe as urinary retention or delirium may result.

Five studies published since 1983 involving a total of 330 patients treated with high-potency antipsychotic drugs have shown that anticholinergic agents are effective in preventing dystonia in the first week of treatment. On average, patients not receiving prophylaxis in these studies were 5.4 times more likely to suffer dystonia than were those who were. In some of these investigations, drug-induced parkinsonism was studied and shown to be prevented or reduced during the treatment of acute episodes when prophylaxis was used. Data on akathisia are less certain, perhaps because the most effective therapies for akathisia, β-blocking agents such as propranolol hydrochloride, have only recently come into common use and have not been studied for prophylaxis.

Care should be taken in selecting patients for prophylaxis against extrapyramidal syndromes. In judging the likelihood of an extrapyramidal syndrome developing, several factors should be considered. A recent study of multiple treatment episodes in schizophrenic patients concluded that patients with a history of extrapyramidal syndromes are at greater risk for future episodes and that this predisposition outweighed other risk factors. In that investigation, history was an accurate predictor of a future occurrence of the syndrome in 84% of patients. Age is a significant risk factor. Younger patients treated with neuroleptic agents are more likely to have dystonic reactions than older patients. Middle-aged patients may be more susceptible to the occurrence of akathisia. More recent data show that young, as well as older, patients are also in danger of drug-induced parkinsonism.

The dosage and potency of the antipsychotic medication must be considered as well. Patients treated with high-potency drugs such as haloperidol are at a higher risk for

extrapyramidal syndromes than those treated with low-potency agents such as thioridazine. Low doses of neuroleptic agents generally lower the incidence and severity of the disorders. Dystonia, unfortunately, can appear at low antipsychotic doses and may be recurrent so that, even at low antipsychotic doses, prophylaxis may be needed.

Several circumstances may make the development of extrapyramidal syndromes especially undesirable. Paranoid patients for whom the therapeutic relationship is tenuous are one example. The development of these syndromes would be particularly harmful in patients requiring orthopedic devices such as neck braces or casts. These considerations should enhance the prescribing of prophylaxis. On the other hand, this prophylaxis is relatively contraindicated in patients who may be harmed by anticholinergic side effects such as impaired recent memory. Older patients receiving low-potency antipsychotic agents are unlikely to benefit from prophylaxis. Patients with deficits in short-term memory from head trauma, dementias, and other causes are not good candidates for prophylaxis as they are more likely to suffer further memory impairment and may become delirious.

The withdrawal of prophylactic medication should be attempted after the initial treatment has been completed if the patient is free of symptoms and the antipsychotic regimen has been stabilized. Studies have shown that some patients will have recurrent episodes and deterioration of mental status when anticholinergic therapy is withdrawn. For this reason, the withdrawal of prophylactic agents should be gradual and carefully monitored.

GEORGE A. KEEPERS, MD
Portland, Oregon

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Panic Disorder

THOUGH PANIC DISORDER and panic disorder with agoraphobia or phobic avoidance (PDA) are common (the mean lifetime prevalence of panic disorder is 1.5%), the diagnosis is frequently missed: 70% of patients with PDA in one large study had more than ten medical consultations before receiving the correct diagnosis and treatment.

The "classic" presentation of panic disorder consists of sudden, unexpected, discrete attacks of intense fear or discomfort without a recognizable precipitant, accompanied by at least four of the following symptoms during at least one of the attacks: dyspnea or smothering sensations; dizziness, unsteadiness, or faintness; palpitations or tachycardia; trembling or shaking; sweating; choking; nausea or abdominal distress; depersonalization or derealization; numbness or paresthesias; flushes or chills; chest pain or discomfort; fear of dying; and fear of going crazy or doing something uncontrolled. Panic disorder, however, frequently occurs with symptoms referable to only a single organ system. Such single system presentations include chest pain and dyspnea (33% to 59% of patients seen because of chest pain but with no abnormalities found on coronary angiography were found in three different studies to have PDA); balance disorder ("dizziness") without true vertigo (25% to 50% of patients seen because of vestibular disorder symptoms have a subtype of panic disorder); abdominal discomfort, pain, and diarrhea (about 33% of patients seen by gastroenterologists were found to have PDA).

Large-scale clinical studies have shown that for most patients, PDA is a chronic relapsing disorder. Multiple family and twin studies show that panic disorder has a highly familial transmission with a strong genetic component (31% monozygotic concordance, 0% dizygotic concordance).

Panic disorder with agoraphobia has a startlingly high comorbidity and mortality. Patients with untreated PDA attempt suicide at a rate equivalent to that of patients with major depression (15% to 20% of patients). This disorder has a dramatically high incidence of comorbid major depression, alcohol abuse, substance abuse, other anxiety disorders, multiple phobias or agoraphobia, cardiovascular disease, and personality disorders. Patients with PDA experience substantially more impairment in social, family, and occupational functioning than the general population.

The proven standard of effective treatment for PDA continues to be pharmacotherapy to stop and prevent recurrent panic attacks, plus behavior therapy (exposure in vivo) for any phobic avoidance that may remain once the panic attacks have been stopped. Most clinical studies have found the first-generation tricyclic antidepressants, the monoamine oxidase inhibitors, and two of the benzodiazepines (alprazolam [Xanax] and clonazepam [Klonopin]) highly effective in stopping and preventing recurrent panic attacks when maintained at therapeutic blood concentrations. Of the newer antidepressant medications, fluoxetine (Prozac) and clomipramine hydrochloride (Anafranil) have demonstrated efficacy in PDA, whereas buproprion hydrochloride (Wellbutrin) and the nonbenzodiazepine anxiolytic buspirone hydrochloride (BuSpar) have not.

The goal of appropriate pharmacologic management is the complete absence of all panic and subpanic attacks. This can be achieved with a single medication in more than 85% of patients, though it may take several treatment trials to find the best medication. Refractory cases may require more complicated protocols.

Recent reports of two nonpharmacologic treatments, cognitive therapy and cognitive-behavioral therapy, show promise for some patients with PDA.

The core of cognitive-behavioral treatment is systematic structured exposure to the feared internal sensations, coupled with cognitive procedures to restructure anxiety-provoking thoughts, catastrophic misinterpretations, and faulty core beliefs. The therapist directs the patient to induce the somatic sensations typical of a panic attack (dizziness, tachycardia, dyspnea, chest tension) in the office (by having the patient spin around, run in place, hyperventilate, or contract chest muscles tightly), while together therapist and patient critically examine the symptom experience, correct the patient's frightening and catastrophic cognitive misinterpretations of the sensations, and control the symptoms with a variety of relaxation techniques. The patient practices at home what is learned in the office and keeps a daily diary of symptoms, reflex cognitive distortions, and corrective thinking and behavior.

Reports of the nonpharmacologic treatment of PDA to date review small treatment populations and short follow-up

periods. The few studies comparing the efficacy (short- and long-term) of pharmacologic and nonpharmacologic treatments suffer from a variety of conceptual and methodologic difficulties. These include a failure to differentiate patients with panic disorder from those with panic disorder and agoraphobia or those with subtypes of panic disorder, and the heterogeneity of diagnostic criteria, treatment procedures, and measures of clinical success. Thus, our present state of knowledge does not enable us to predict accurately which patients will do best with which treatment(s) or how different treatments might best be integrated.

Patients with PDA should be educated regarding the various treatment options available. The choice of treatment will depend on the training and expertise of the clinician, the availability of specialists, a patient's sense of urgency, available resources, and the preferred type of treatment. If nonpharmacologic treatment is elected, those patients who are not completely relieved of panic attacks after an adequate treatment trial (three months), or who relapse after treatment, should receive appropriate pharmacologic therapy for panic, combined with exposure treatment of phobic avoidance.

DOUGLAS KAHN, MD
Newport Beach, California

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Rational Polydrug Use in Psychiatry

SINGLE-DRUG THERAPY has been the standard for psychopharmacology for the past two decades. This approach is based on clinical studies that excluded multiple drug therapies to decrease variance in the results. There is consensus, however, that 20% to 40% of patients with depression, manic-depressive illness, anxiety disorders (panic disorder and obsessive-compulsive disorder), and schizophrenia either do not respond initially or do not maintain a response to standard single-drug regimens.

Few double-blind placebo-controlled studies have tested polydrug regimens because a large number of patients would be required to achieve statistical significance. We have to rely mainly on case series and reports based on pharmacologic theory or empiric findings. The reasons to use several drugs include a nonresponse to monodrug therapy; the need for imminent clinical remission (from either patient suffering or the financial limitations of waiting for serial therapies to work); the different therapeutic sites of action of multiple agents; additive or multiplicative effects; and the avoidance of side effects. For example, acute mania appears to respond faster, with better patient compliance, and with fewer side effects when a potent benzodiazepine (usually lorazepam or clonazepam) is temporarily added to a regimen of neuroleptic and antimanic agents. In labile manic-depressive illness, prophylaxis with an anticonvulsant (valproate or carbamazepine) or verapamil enhances stability.

Patients with depression that does not abate in three to four weeks with standard antidepressant therapy commonly will have lithium, thyroid, or stimulants added to the regimen. These agents work independently, and several may be used for refractory cases. Some antidepressants produce side effects that can be countered by others. Because the therapeutic effect is additive, two antidepressant heterocyclic reuptake inhibitors can be administered concurrently. This is commonly done when agitation or insomnia occurs with the use of fluoxetine or desipramine by adding trazodone or another sedating agent, such as doxepin or amitriptyline, at night. Although panic disorder often responds to the use of a single agent (such as alprazolam, phenelzine sulfate, or imipramine hydrochloride), subtle fluctuations in anxiety may continue and increase anticipatory anxiety to a disabling degree. Hence, adding the other agent(s), which act through separate mechanisms, is frequently required. A pharmacologic plateau of obsessive-compulsive disorder to the use of clomipramine or fluoxetine may take 12 weeks to occur, with a third of patients not responding. Serotoninergic activity is augmented by adding the other primary drug or buspirone hydrochloride (as much as 100 mg per day), lithium, or fenfluramine hydrochloride.

Schizophrenia is not a unitary disease, but neuroleptics all appear to have equivalent efficacy. Polydrug therapy with older neuroleptics plus clozapine has increasing appeal but few data to support its use. Neuroleptic side effects contribute importantly to noncompliance and morbidity, however. In addition to the well-appreciated use of anticholinergics, the recent understanding of akathisia has led to a low threshold for the use of propranolol hydrochloride (20 to 80 mg per day in divided doses) for this extrapyramidal syndrome of anxiety and motor restlessness. The augmentation of neuroleptic therapy has proved beneficial with the use of carbamazepine, lithium, or benzodiazepines in some schizophrenic patients. Although no specific subgroup is predictably responsive, it is commonly thought that these drugs are relatively more effective in patients with active psychotic symptoms, aggression, or schizoaffective schizophrenia.

The use of several hypnotic agents in a single patient is usually based on their half-life. In selected patients with pronounced difficulty falling and staying asleep, an ultrashort-acting hypnotic (triazolam, for instance) may be beneficial when combined with a longer-acting agent, and the combination has reduced morning sedative side effects.

In these uses of polydrug therapy, each agent is prescribed systematically and for a specific target behavior that can be evaluated for response. This rational use of multiple drugs is therefore valid. It is distinct from older, fixed-dose combination drugs or simplistically adding virtually identical agents without careful reasoning. The search for therapeutic benefit must be tempered by caution about additive side effects such as anticholinergic or hypotensive effects.

ROBERT GERNER, MD
Los Angeles, California

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Tobacco Dependence and Smoke-free Psychiatric Units

THE UNITED STATES is undergoing a no-smoking trend, with a decrease in the proportion of the general population that smokes and an increase in the number of health facilities being designated as smoke-free. Despite the national move toward quitting smoking, 60% to 80% of patients admitted to psychiatric units have tobacco dependence. More than half of the adult psychiatric hospitals in the greater Denver area are currently designated as nonsmoking, and additional units are planning or strongly considering going smoke-free. The high rate of smoking by psychiatric patients and the decreased accessibility to a smoking area while in hospital places these patients at risk for nicotine withdrawal.

Nicotine withdrawal symptoms commonly include anger, anxiety, irritability, a craving for cigarettes, difficulty concentrating, hunger, impatience, and restlessness. They are most prominent during the first 24 to 48 hours following smoking cessation. This timing generally coincides with the most restrictive period of a hospital stay. Seclusion or restraints may prevent a patient from being able to smoke even on a ward that provides a smoking room or area. Restricted privileges even after someone is no longer requiring seclusion or restraints may continue forced smoking cessation.

A number of investigators have evaluated pharmacologic approaches to treating smokers who wish to stop. Few have studied treating nicotine-dependent psychiatric patients in a nonsmoking unit. Pharmacologic approaches include nicotine replacement, such as nicotine gum and transdermal patch, nicotine antagonists such as mecamylamine hydrochloride, and supportive agents that symptomatically treat withdrawal symptoms such as clonidine hydrochloride and doxepin hydrochloride.

Nicotine gum or nicotine polacrilex (Nicorette), the only available replacement agent in the US, ameliorates many of the symptoms associated with tobacco withdrawal. Unfortunately, for its appropriate and safe use, detailed instructions must be followed. Given that many psychiatric patients are psychotic, depressed, confused, or otherwise cognitively impaired on admission, correct self-administration may not be possible.

A nicotine transdermal patch currently being tested in the United States may alleviate some of the difficulties of using nicotine gum. Well tolerated and simpler to use, the nicotine patch may be a useful adjunct in treating nicotine-addicted psychiatric patients. Nicotine antagonists may be helpful in preventing relapse but appear to have no appreciable role in treating acute withdrawal in psychiatric inpatients.

Of the supportive agents, clonidine appears most useful in diminishing nicotine withdrawal symptoms, including craving. The transdermal form of clonidine is less likely to produce the adverse side effects, such as postural hypotension, that may occur with oral clonidine use. Clonidine and nicotine gum seem to be a beneficial combination. Other supportive agents, including doxepin, fluoxetine, and buspirone hydrochloride, may be helpful, but patients must be pretreated for two to four weeks before actually stopping cigarettes for these medications to be effective.

In addition to the pharmacologic approach, education and support are important interventions, particularly for patients who truly wish to quit smoking. Mere advice from a physician to quit smoking increased cigarette abstinence at one year from 0.3% to as much as 5%. Staff can provide support and training in social skills, stress management, and relaxation techniques. Inpatient smoking cessation groups or individual education may further enhance long-term abstinence.

In the recent past, cigarettes were used by staff at institutions as a form of token economy, which may have contributed to the high prevalence of tobacco use in the psychiatric population. Mental health professionals should help nicotine-addicted patients break their habit.

JOHN A. MENNINGER, MD
Denver, Colorado

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Eating Disorders in Psychiatric Illness

EATING DISTURBANCES may be part of and related to specific clinical symptoms of formal psychiatric disorders. Examples include anhedonic appetite loss in severe depression, delusional aversion to food in psychotic disorders, and appetite loss consequent to stimulant drug abuse. Recent studies confirm a strong coupling of carbohydrate preference and intake and hyperphagia with depressive mood in seasonal affective disorder that can be reversed with light therapy and season change. A study of the direction and extent of weight change during unipolar depression in unmedicated patients found consistency from one episode of depression to another. Direction and extent of weight change appeared to be an independent, stable patient characteristic that might be a marker for the clinical subtype unrelated to severity or endogenous features.

Appetite regulation, food selection, and consummatory behavior are modulated on a neurobiologic level by the same neurotransmitter systems that are principally involved in psychiatric disorders. Psychopharmacologic agents used in treatment are frequently associated with the stimulation or suppression of appetite and physical activity, both of which affect feeding, satiety, and weight loss or gain. A nutrition assessment for all patients with psychiatric disorders should include physical and laboratory screening for malnutrition, unusual eating habits, belief systems regarding foods, and the effect of physical illness and medications on nutritional status. Extreme deviations in dietary intake may alter nutritional substrates, adversely affecting the clinical course of psychiatric illness or the therapeutic efficacy of medication. An iron deficiency, for example, decreases the concentration of dopamine D_2 receptors, possibly diminishing the efficacy of medication for certain depressive disorders. Also, an experimental reduction of tryptophan in the diet of depressed patients magnified symptoms and reversed the therapeutic effect of antidepressants.

Other serious eating disturbances associated with psychiatric illness include globus hystericus, swallowing distress, and cyclic vomiting (somatoform disorder); choking phobia, anorectic states, and anorexia nervosa or bulimia nervosa (or both) associated with sexual abuse and obsessive-compulsive

disorder (anxiety disorder); pica, hyperphagia, and delusional anorexia (schizophrenia); hyperphagia and bulimia nervosa (borderline personality disorder); anorexia nervosa (Tourette's disorder); hyperphagia, pica, and rumination (mental retardation); hyperphagia (atypical depression); and severe appetite decrease and rumination (melancholia). In depressive states, the degree of the eating disturbance may be related to the severity of the depressive disorder. In anxiety disorder, the degree of anorexia is more severe in association with depression.

To arrive at a diagnosis, it is important to distinguish between eating disturbances associated with primary psychiatric disorders and the comorbid occurrence of a primary eating disorder (anorexia nervosa and bulimia nervosa) and major psychiatric disorders. This distinction is not always clinically apparent and awaits clarification by future research.

Anorexia nervosa and bulimia nervosa are characterized by considerable self-regulatory psychopathology with profound disturbances in self-representation, self-esteem, and self-stability. There is often a relentless drive toward thinness and reactive counterweight behaviors (self-induced regurgitation, laxative abuse, and exaggerated exercise pattern) in the context of a cognitive preoccupation with food selection, body experience, and weight. Secondary restrictive and hyperphagic eating disturbances seen in major psychiatric disorders are often initially less evident than the more dramatic primary signs of profound mood changes, psychosis, and suicidal behavior.

Eating disorders are not merely "variants" of an affective disorder. A spectrum of clinical features from mild dysthymia to major depression may be associated with a wide range of disturbed eating behavior. A recent positron emission tomographic study (glucose brain metabolic function) found considerable differentiation of cerebral metabolic patterns between women with bulimia nervosa or a depressive disorder and a normal control group. Several lines of research have noted a more extensive eating disturbance (both anhedonic restriction and hyperphagia) correlated with the severity of both the formal eating disorder and the associated primary psychiatric disorder. The most frequent comorbid disorders associated with anorexia nervosa and bulimia nervosa are affective disorder, obsessive-compulsive disorder (17% lifetime incidence of eating disorders), substance abuse, and posttraumatic stress disorder (sexual abuse and victimization). A more detailed understanding of the genetics, clinical manifestations, and complications of comorbidity in the eating disorders may lead to more effective therapeutic interventions in heretofore treatment-resistant patients.

BARTON J. BLINDER, MD, PhD
Newport Beach, California

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Nocturnal Enuresis

NOCTURNAL ENURESIS is often considered a result of psychological conflict. Unconscious sexual fears, passivity, exhibitionistic traits, hate for the opposite sex, effeminacy, and castration fears have been mentioned as some psychological causes. Parental inconsistency, punitive or lax toilet training, maternal anxieties, or paternal aloofness have also been implicated. Many pediatricians still send enuretic children to child psychiatrists for therapy once organic causes have been ruled out. Psychotherapy, however, has not been shown to resolve bed-wetting except for the expected spontaneous cure rate.

Bed-wetting shows a high spontaneous cure rate; it occurs in a third of children at age 4, drops to 10% at age 6, and decreases by 15% per year thereafter.

Two major types of bed-wetting can be distinguished. Primary enuresis accounts for 80% of patients who wet their beds. The main causes are physiologic variations of functional bladder capacity, bladder sphincter muscle control, or sleep disturbance. A strong genetic factor is often apparent. In secondary enuresis, bladder control had been gained but then was lost—mostly due to regression in response to a stressful event. In some instances, secondary emotional problems develop. Most enuretic children, however, do not show primary or even secondary emotional disturbance.

New, developmentally based approaches have dramatically changed the assessment, treatment, and severity of the psychological consequences of enuresis. Treatment options need to take spontaneous resolution into account.

Education is one available method. To relieve unnecessary feelings of guilt and blame, it is important to help the parents and the child understand that bed-wetting is a developmental rather than an emotional problem. For children younger than 6, reassuring parents by stressing the self-limited nature of the problem for most children may be sufficient. For children older than 6, bed-wetting can be embarrassing; therefore, most can easily be counseled to become active participants in their treatment. Restricting fluids and urinating before bedtime may increase the number of dry nights and give a motivating sense of success. Parental management of enuresis should be nonpunitive; dry nights should be praised; wet nights ("accidents") should be handled matter-of-factly with agreements on who should clean the sheets and pajamas. Parent-child education alone leads to noticeable improvement in 70% of enuretic children. Bladder stretching and urine stream interruption exercises have a cure rate of about 35%. Bed-wetting alarms are most effective in children older than 8 years and show a cure rate of 70%. They should be used until three weeks of continuous dryness are achieved.

The use of medications in the treatment of enuresis is controversial. Only imipramine hydrochloride, a tricyclic antidepressant, has been extensively studied. Low dosages (50 to 75 mg at bedtime) are required; while notable improvement has occurred in half of the treated children, relapse rates after the drug is discontinued are high, and a cure rate of only 25% can be expected. Because of the high toxicity of antidepressant agents and their limited effectiveness, their use is rarely indicated.

More success with no recognizable adverse effects has recently been described with the nightly intranasal use of 20 to 40 μg of desmopressin acetate, an antidiuretic agent. Des-

mopressin use causes immediate improvement in 70% of enuretic children; relapse rates are lower than with the use of imipramine but higher than with bed-wetting alarms.

Secondary regressive enuresis responds best to crisis intervention to help the child and family cope with the identified stress that triggered the bed-wetting episode. Counseling as to the transient nature of the bed-wetting problem may prevent a more serious maladaptive response.

EBERHARD M. MANN, MD
Honolulu, Hawaii

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Treatment-Resistant Depression

THE BEST ESTIMATE IS THAT about 20% of depressed patients do not respond adequately to treatment. As the debilitating effects of depressive disorders on patients and their families become more apparent, it is important to develop effective pharmacologic strategies for patients whose depressions are resistant to treatment. Physicians have been hampered, however, by a lack of consensus in defining treatment resistance. It is clear that treatment intolerance—the inability to tolerate one or more antidepressant agents in sufficient doses to effect a response—needs to be distinguished from true treatment resistance. Beyond that, whether treatment resistance should be defined by a level of symptoms for a certain period of time or by a failure to respond to a number (but how many?) of antidepressant drugs at specified doses or plasma concentrations is still debated. Similarly, some authors have suggested that patients not be called treatment resistant until they have had a trial of electroconvulsive therapy, and others see electroconvulsive therapy as a strategy for patients already defined as treatment resistant.

Among patient characteristics that may predict treatment resistance, the presence of other concomitant disorders is the most important. Patients who both are depressed and have drug or alcohol abuse, severe personality disorders, or active significant medical illness have lower response rates to antidepressant treatments.

Although there are a variety of creative pharmacologic strategies for treating refractory depressions, the most important recommendations involve using the more common treatments correctly. As an example, patients should not be considered treatment resistant until they have had a trial of one tricyclic antidepressant at a dosage level of imipramine hydrochloride, 300 mg per day, or its equivalent for at least six weeks. With some antidepressants, determining trough serum concentrations of the tricyclic prescribed (the blood specimen to be drawn in the morning after nighttime dosing) and adjusting the dose according to the serum level will further enhance the adequacy of treatment. A substantial number of patients referred to as treatment resistant will not meet even this first criterion because many clinicians stop an antidepressant medication after three or four weeks of treatment, a strategy that will decrease response rates by as much as 25%.

Patients who have not responded to an adequate trial of one tricyclic antidepressant should be treated using any one (or all four, if no response is seen) of the following strategies: adjunctive medications such as lithium carbonate added to the tricyclic regimen; switch to a cyclic antidepressant of a different class, such as fluoxetine; switch to a monoamine oxidase inhibitor antidepressant (this is probably the most underused effective strategy); or electroconvulsive therapy (for more severely depressed patients). For those patients treated with fluoxetine first, the tricyclic antidepressant would simply be substituted in its place.

Only if these basic strategies fail should the more unusual therapies, such as stimulants, combined tricyclic and monoamine oxidase inhibitor antidepressants, combined fluoxetine and tricyclics, or the anticonvulsants be tried.

MICHAEL J. GITLIN, MD
Los Angeles, California

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Antidepressant Treatment in Patients With Heart Disease

THE GROWING RECOGNITION that substantial medical morbidity and mortality are associated with depression has led clinicians to treat depression in patients with coexisting serious medical disorders if it can be done safely. Because cardiac toxicity of antidepressant treatment may be the most serious concern for clinicians, it is important to review recent advances that have increased the safety of treating depression in patients with heart disease.

The most serious complication requiring caution is a conduction disturbance, especially left bundle branch block or hemiblock. Tricyclic antidepressant agents have a quinidine-like (class IA antiarrhythmic) effect, slowing conduction and potentially causing complete heart block. Indeed, complete heart block and arrhythmias are the probable causes of death in tricyclic overdose. The use of tricyclic antidepressants is contraindicated in the presence of left bundle branch block or hemiblock but not right bundle branch block because of the latter's small size. They may have additive toxicity with other class IA antiarrhythmic agents including quinidine, procainamide hydrochloride, and disopyramide phosphate. An additional problem is that the slowed metabolism of tricyclic antidepressants can exacerbate side effects including orthostatic hypotension. Trazodone may be given to patients with conduction disturbance with careful monitoring. The same may be true for fluoxetine, buproprion hydrochloride, monoamine oxidase inhibitors, and psychostimulants (methylphenidate and others).

The use of tricyclic antidepressants is generally safe in patients with ventricular ectopy because of their quinidine-like antiarrhythmic actions. In contrast, trazodone may exacerbate preexisting ventricular arrhythmias for unknown reasons. Until further research is done on this problem, trazodone should generally not be used in this context.

Antidepressant therapy is generally safe in patients with diminished cardiac contractility, as these medications do not appear to have a negative inotropic effect. Patients with ejec-

tion fractions at or below 20%, however, should be carefully monitored as a precautionary measure.

Two new antidepressants, fluoxetine and buproprion, appear to have a decreased potential for cardiotoxicity. To date, no reports of cardiotoxicity with the use of these medications have appeared in the literature. It should be noted that premarketing trials have been carried out on depressed patients with normal hearts, so the safety of these medications in patients with organic heart disease remains to be determined.

The safest antidepressant treatment in depressed patients with serious heart disease is electroconvulsive therapy. Although heart rate and blood pressure increase considerably during the first few minutes following the electrical stimulus using standard anesthetic techniques, creating a potential danger for a patient with a vulnerable myocardium, electroconvulsive therapy has been shown to induce only a minimal rise in these variables with the use of intravenous labetalol hydrochloride or trimethaphan camsylate (Arfonad) at the time of anesthesia induction.

RICHARD D. LANE, MD
Tucson, Arizona

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Obsessive-Compulsive Disorder

OBSESSIVE-COMPULSIVE DISORDER had, until recently, almost always been resistant to treatment. Selective serotoninergic antidepressants and behavioral therapy techniques now allow these disorders to be treated successfully.

Several double-blind placebo-controlled trials have shown fluoxetine hydrochloride (Prozac), fluvoxamine, clomipramine hydrochloride (Anafranil), and buspirone hydrochloride (BuSpar) to be effective medications. About 70% to 80% of the patients in these trials had a 45% to 55% decrease in their symptoms. In clinical terms, this meant that a patient who had spent every hour of every day locked into the performance of meaningless rituals was, after treatment, having only occasional (about once an hour) obsessive thoughts and was usually able to resist performing a compulsive ritual without an excruciating increase in anxiety. Most patients felt treatment had reduced symptoms to the point that they no longer interfered in their social or occupational functioning.

The most effective agents currently available are fluoxetine and clomipramine. The key to effective treatment with these drugs is to use a dosage schedule for a sufficient period before deciding whether a patient is treatment responsive. With clomipramine, this means using an average oral dosage of 200 mg per day (therapeutic range, 100 to 250 mg) for at least eight weeks. Patients may show little or no therapeutic response at six weeks, yet go into relative remission at eight weeks. Treatment begins at 25 mg per day and increases by 25 mg every three days, leveling off at 200 mg per day. In patients prone to panic attacks, an initial dose of 10 mg per day is used to lower the risk of inducing panic or excessive anxiety.

The dosing strategy with fluoxetine is somewhat different. A wide range of oral doses has been reported to be effective. Consequently, most regimens should be started at 20 mg per day, increasing the dose by 20 mg every six weeks. In rare instances, the dosage may be pushed to as high as 100 mg per day, but usually 40 mg per day is a therapeutic dose.

In cases refractory to treatment, even after the addition of behavioral therapy, a variety of adjunctive and combination treatments may be used, including buspirone, lithium carbonate, monoamine oxidase inhibitors, trazodone hydrochloride, alprazolam, and fenfluramine hydrochloride. There is some evidence that buspirone may be an effective agent alone at doses averaging 60 mg per day. Nevertheless, a subgroup of patients with classical obsessive-compulsive disorders, who are suffering from neither schizophrenia nor personality disorders, remain refractory to treatment. For this subgroup, a neurosurgical procedure, limbic leukotomy, has at times proved effective.

DAVID L. FOGELSON, MD
Santa Monica, California

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Brain Imaging and Neurodevelopmental Psychiatry

NEURODEVELOPMENTAL PSYCHIATRY is gaining increasing recognition as an important theoretic approach to understanding the cause of many serious psychiatric disorders. In the past, investigators focused primarily on psychological, environmental, and genetic factors to explain psychiatric disturbance. The recent development of neuroimaging technologies for in vivo investigation has expanded knowledge of the neuropathy and physiology in such disturbances as schizophrenia, affective disorders, autism, obsessive-compulsive disorder, and attention-deficit disorder. Many of these findings confirm the presence of neuropathology that developed before the onset of the disorder.

Modalities used to image the brain include computed tomography, magnetic resonance imaging and spectroscopy, computed encephalography, positron emission tomography, and single photon-emission computed tomography. Of these neuroimaging techniques, magnetic resonance imaging (MRI) and magnetic resonance spectroscopy are uniquely suited to study structural, physiologic, and developmental brain abnormalities in children because they involve no ionizing radiation or radioactive isotopes and have been shown to have no biologic hazards at currently used field strengths. Magnetic resonance imaging offers superior grey-white matter delineation and excellent visualizations of midline structures. As an example, MRI studies of autistic children show posterior fossae abnormalities (cerebellum, fourth ventricle, and brain stem) compared with normal controls.

Neuroimaging has been particularly useful in the study of schizophrenia. An increasing number of studies find abnormal brain structure and function in adult schizophrenic patients compared with normal controls. These abnormalities include a larger ventricle to brain ratio; enlargement of the

lateral and third ventricles; decreased size of the temporal lobe including the hippocampus and amygdala; changes in the corpus callosum; and physiologic changes in blood flow and glucose use in the prefrontal cortex. Many of these studies report greater changes on the left than on the right. It is frequently suggested that these structural changes are present before the onset of the schizophrenic disorder and may be present prenatally or in early childhood. In a recently published MRI study, children with a disorder in the schizophrenia spectrum were found to have larger left than right frontal horns of the lateral ventricles. The schizophrenic-spectrum children also had more nonspecific MRI abnormalities than the psychiatric controls.

Thus, neuroimaging technologies are making it possible to begin to understand the connection between behavior and brain structure and function. This understanding may make it possible to develop effective prevention, early intervention, and treatment programs for patients with serious psychiatric disorders.

ROBERT L. HENDREN, DO
Albuquerque, New Mexico

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Treating Compulsive Behaviors in Dermatology

PATIENTS WITH STRONG COMPULSIVE TENDENCIES are often seen by dermatologists. These patients can be divided into two groups. The first consists of those who do not have any primary skin disease. The skin changes are self-induced and are dermatologic manifestations of compulsive behavior. The second group is patients who have primary skin disorders exacerbated or perpetuated by compulsive behavior such as scratching, rubbing, and picking.

The first group includes patients with trichotillomania, who compulsively pull out their hair; onychotillomania, who pick on their nails; and compulsive hand washers. The more common examples of the second type of patients include those with lichen simplex chronicus (neurodermatitis) and prurigo nodularis. In lichen simplex chronicus, the patient has a powerful compulsion to scratch at a patch of skin that is intermittently itchy; eventually this patch of skin becomes thick and rough from trauma, often persisting for years. In prurigo nodularis, the patients have hard nodules from chronic excoriation. There are also patients with acne excoriée who compulsively pick on their acne.

The treatment of these compulsive disorders in dermatologic practice has been difficult. The recent emergence of psychopharmacologic agents with anticompulsive effects may substantially improve the treatment of these disorders. Among the medications with definite or postulated anticompulsive efficacy, clomipramine hydrochloride (Anafranil) has the best documentation regarding anticompulsive efficacy; it is also the only medication that is currently approved by the Food and Drug Administration (FDA) for this purpose. Clomipramine is a tricyclic antidepressant and, like other tricyclic agents, the dosage must be titrated until an optimal regimen is reached. The usual maximum dosage for adults is 250 mg per day and for children, 3 mg per kg per day. Clomipramine has side effects similar to other tricyclic antidepressants such as dry mouth, constipation, blurred vision, postural hypotension, and a lowered seizure threshold.

Other medications that are not FDA approved for the treatment of obsessive-compulsive disorder but that are currently undergoing extensive clinical trials to determine efficacy include fluoxetine (Prozac) and fluvoxamine. Both of these agents are powerful inhibitors of serotonin reuptake; unlike clomipramine, however, they lack significant affinity for histaminic, cholinergic, and α-adrenergic receptors and have a different side effect profile.

It should be noted that these medications are not "magic bullets." Treatment with medication alone is not adequate unless a patient is motivated to stop the damaging compulsive behavior. On the other hand, if the patient is properly motivated to stop, these medications appear to decrease the compulsive urge and thereby allow the patient to prevail in the determination to stop. Last, whenever feasible, a multidisciplinary approach to the treatment of chronic compulsive disorders in dermatology is always preferable to relying on pharmacotherapy alone. For instance, a clinical psychologist with a background in behavioral therapy may use techniques such as response prevention, response substitution, and "flooding" to modify the behavior.

JOHN Y. M. KOO, MD
San Francisco, California

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Bulimia Nervosa

BULIMIA NERVOSA is a disorder characterized by repeated and frequent episodes of binge eating large quantities of food—at least two episodes per week for a period of at least three months—often followed by purging, usually by inducing vomiting, but also by using laxatives, emetics, and diuretics. Patients are preoccupied with weight and feel unable to resist the urge to binge eat. About 95% of sufferers are women, and, although most are at normal weight, the disorder may also be seen in extremely thin patients with anorexia nervosa. About 25% of obese patients are estimated to binge eat in a manner similar to that of some patients with bulimia nervosa, but they do not purge. Although the prevalence of clinically unmistakable bulimia nervosa is estimated at between 1% and 3% of college-aged women, many more women have "subclinical" disorders. The disorder is most common among middle- and upper middle-class white women, although an increasing number of less affluent and of minority patients are being seen. Frequent associated disorders include depression (50% to 75%) and alcoholism or other substance use disorders (about 30%). These patients also often exhibit dramatic personalities and impulsive behaviors involving overspending, sexual behaviors, and shoplifting. Family histories often reveal mood disorders, alcohol and substance abuse, and eating disorders.

Patients are often secretive about their problems. Clinical features to raise suspicion include weight and diet preoccupation in normal-weight women, swollen salivary glands (giv-

ing the face a squirrel-like appearance), the erosion of dental enamel, especially of the front teeth, scarring on the dorsum of the hands and fingers, and unexplained chronic diarrhea and "irritable bowel." Abnormal laboratory test values may include alkaline urine, an elevated serum amylase level, and mild hypokalemic hypochloremic alkalosis.

Admission to hospital is rarely indicated for uncomplicated cases. Treatment should focus on restoring good dietary habits. Education, nutritional counseling, and cognitive-behavioral and insight-oriented therapies should be administered by registered dieticians and by psychiatrists or psychologists familiar with eating disorders. Support groups are often helpful. For patients with persistent depression and those who fail to respond to psychoeducational intervention within a few months, antidepressant medications such as fluoxetine (20 to 80 mg per day) and imipramine hydrochloride (150 to 300 mg per day) have proved useful.

JOEL YAGER, MD
Los Angeles, California

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Alerts, Notices, and Case Reports

Aspergillar Myocarditis and Acute Coronary Artery Occlusion in an Immunocompromised Patient

MICHAEL K. HORI, MD
Sacramento, California

LAWRENCE L. KNIGHT, MD
PAULA G. CARVALHO, MD
DENNIS L. STEVENS, PhD, MD
Boise, Idaho

INVASIVE ASPERGILLAR infections have increased in frequency in proportion to the increasing number of severely immunocompromised patients. A characteristic of aspergillar infection is the invasion of blood vessels with resultant tissue necrosis.

Infections of the coronary arteries leading to vessel damage are rare. We report the case of a patient with aspergillar myocarditis in whom fatal acute coronary artery occlusion and myocardial necrosis developed with associated electrocardiographic and hemodynamic findings.

Report of a Case

The patient, a 45-year-old man, was admitted for increasing dyspnea, wheezing, and a productive cough of 12 hours' duration. The patient had suffered from severe asthma for 12 years, had required continuous corticosteroid therapy for the past six years, and had type II diabetes mellitus, treated with oral hypoglycemic agents. On physical examination, he appeared cushingoid and in moderate respiratory distress. The findings included a respiratory rate of 36 per minute with diffuse expiratory wheezes, decreased breath sounds, and fine right basilar rales. There were no abnormal cardiovascular findings. The laboratory evaluation revealed hypoxia, with blood gas determinations done with the patient breathing room air showing a Po_2 of 57 mm of mercury (7.58 kPa), a Pco_2 of 45 mm of mercury (5.98 kPa), and a pH of 7.46. The leukocyte count was 8.5×10^9 per liter (8,500 per μl) with 0.86 granulocytes, 0.06 band forms, 0.04 lymphocytes, and 0.04 monocytes. The chest radiograph did not show infiltrates, cardiomegaly, or congestive heart failure. The electrocardiogram showed sinus tachycardia with nonspecific ST-T wave changes. A sputum Gram's stain showed rare polymorphonuclear leukocytes. The initial sputum culture grew a few colonies of an *Aspergillus* species.

Despite aggressive therapy with bronchodilators, cefuroxime, corticosteroids, and diuretics, the patient required intubation because of respiratory failure and subsequently had intermittent fever. Cultures of blood and urine were sterile and of sputum grew *Pseudomonas maltophilia*. A regimen of the combination product trimethoprim and sulfamethoxazole was started intravenously, and a Swan-Ganz catheter was transiently placed that revealed a cardiac index of between 2 and 2½ liters per minute per m² with a normal pulmonary capillary wedge pressure (PCWP). On the 17th hospital day, transient hypotensive episodes developed with persistent fever, and the patient had a gradual fall in his leukocyte count, platelets, and hematocrit. Blood cultures remained sterile, and sputum smears were negative for acid-fast bacilli. The serum creatine kinase level was 25.0 μkat (1,500 IU) per liter and was exclusively of the MM isoenzyme. Specimens of bone marrow aspirate and biopsy were hypocellular in appearance but without evidence of neoplasia or infection. A regimen of broad-spectrum antibiotics was started, and the trimethoprim-sulfamethoxazole was stopped because of presumed medication-induced bone marrow toxicity. The patient remained febrile and neutropenic. A new, dense, right lower lobe pulmonary infiltrate and patchy, ill-defined infiltrates developed in both lungs, and a course of amphotericin B was initiated for presumed invasive aspergillosis. New unifocal ventricular premature contractions developed, and an episode of atrial fibrillation was also documented. A creatine kinase level was again high and showed exclusively the MM isoenzyme. Two days later the patient had refractory hypotension, with a cardiac index of 1 liter per minute per m² and a PCWP of 24 mm of mercury. His electrocardiogram at this time showed diffusely decreased voltage but no evidence of infarction. Despite ag-

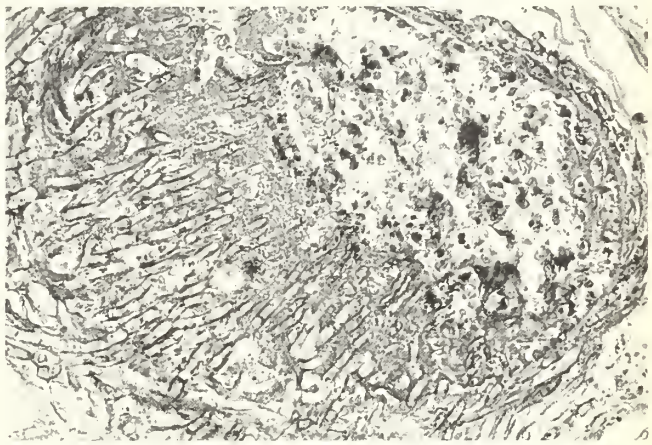

Figure 1.—The photomicrograph shows invasion and occlusion of a coronary artery by fungal organisms with branching septate hyphae (original magnification × 450).

TABLE 1.—*Infections Associated With Coronary Artery Invasion*

Endocarditis
Streptococcus viridans
Streptococcus foecalis or group D streptococcus
Salmonellal bacteremia
Syphilis *(Treponemo pallidum)*
Kawasaki's disease
Aspergillus species
Falciparum malaria (thrombosis rather than invasion)

(Hori MK, Knight LL, Carvalho PG, Stevens DL: Aspergillar myocarditis and acute coronary artery occlusion in an immunocompromised patient. West J Med 1991 Nov; 155:525-527)

From the Department of Medicine, University of California, Davis (Dr Hori), the Department of Medicine, University of Washington School of Medicine, Seattle (Drs Carvalho and Stevens), and the Departments of Medicine (Drs Carvalho and Stevens) and Pathology (Dr Knight), Veterans Affairs Medical Center, Boise, Idaho.

Reprint requests to Dennis L. Stevens, PhD, MD, Chief, Infectious Diseases, Veterans Affairs Medical Center, 500 West Fort St, Boise, ID 83702.

TABLE 2.—*Location of Aspergillar Infections of the Heart*

Series	Patients, No.	Cardiac Locus of Infection			
		Endocardium	Pericardium	Myocardium	Myocardium Plus Endocardium and/or Pericardium
Walsh et al, 1980[7]	17	6	4	4	3
Atkinson et al, 1984[8]	11	1	0	6	4
Young et al, 1970[13]	7	0	2	2	3
Total cases (%)	35	7(20%)	6(17%)	12(34%)	10(29%)

gressive treatment with inotropic agents, the patient died that day.

At an autopsy, examination of the heart revealed that the epicardium and endocardium were free of lesions. The myocardium was homogenous except for a circular hemorrhagic area in the midportion of the intraventricular septum. On microscopic examination, the septum showed a broad zone of acute myocardial infarction marked by extensive myocardial and intravascular invasion by fungal organisms with branching septate hyphae consistent with an *Aspergillus* species. The involved vessel was occluded with thrombus (Figure 1). The rest of the heart and the coronary arteries were unremarkable. Extensive areas of friable, coarsely nodular consolidation were apparent in the pulmonary parenchyma of the left lower lobe and the entire right lung. Several areas of the pulmonary venous system were occluded with dark red thrombotic material. Microscopic examination of the areas of consolidation and thrombosis showed massive involvement by mycelial fungal organisms similar to those found in the heart. The blood vessels of the stomach were also occluded by fungal organisms with resulting mucosal necrosis.

Discussion

Coronary artery microbial infections with vessel damage are unusual. Bacterial mycotic aneurysms with thrombosis or rupture have been described as a complication of *Streptococcus viridans* and enterococcal bacterial endocarditis and of salmonellal bacteremia.[1-3] Medial necrosis of the aorta due to syphilis with the formation of saccular aneurysms may lead to coronary artery obstruction.[4] Kawasaki's disease, a disease of presumed but as-yet-unknown microbial origin, has been associated with coronary aneurysms in 17% of cases (Table 1).[5]

Fungal cardiac infections have been rare in the past but may be increasing in frequency.[6-14] *Aspergillus* species are less frequently identified in patients with heart infections than *Candida* species but are more common than *Mucor* or *Cryptococcus* species and invade the myocardium more frequently than do *Candida* species.[7,8,13] The immune systems of patients with cardiac aspergillar infections are usually compromised. Patients' risk factors include a cardiac or abdominal operation, broad-spectrum antibiotic treatment, immunosuppression from cytotoxic drug therapy, prolonged supraphysiologic corticosteroid therapy, malignant disease, diabetes mellitus, intravenous drug abuse, or prolonged vascular catheter placement.[6,10-12] Aspergillar myocarditis can occur from hematogenous seeding or as a result of spread from the endocardium (usually associated with prosthetic cardiac valve placement) or the pericardium (from contiguous pulmonary infections) (Table 2).[7-9,12,13,15] Myocardial involvement may be limited to rare small abscesses or may be associated with necrosis of large portions of the myocardium due to direct or vascular invasion with consequent ischemic necrosis.[13] Acute myocardial infarction recognized before the development of infection has been described previously in only seven patients.[14] By histopathologic examination, inflammatory infiltration with polymorphonuclear leukocytes is usually seen, but giant cells may be present or an infiltrate may be absent in patients taking cytotoxic drugs.[6,11,14]

This case illustrates some of the clinical aspects of aspergillar myocarditis. First, the contribution of myocardial disease to a patient's illness is often difficult to quantitate because of other contributing factors such as fungal pulmonary disease and drug toxicity.[13] Second, despite vessel involvement, blood cultures rarely show *Aspergillus* species.[6] Third, aspergillar myocardial disease may be associated with considerable hemodynamic compromise with a low cardiac index and a high PCWP,[13] and this may not respond to treatment with inotropic agents or antifungal drugs. Fourth, electrocardiographic changes are usually nonspecific despite extensive tissue damage and may be associated with a new onset of arrhythmias.[6,14] Finally, the creatine kinase MB isoenzyme may not be a useful method of detecting myocardial damage caused by *Aspergillus* species, possibly because of an overwhelming release of non-MB isoenzymes from other infected tissues.

In summary, invasive aspergillosis is one of the rare infectious diseases that may lead to coronary artery compromise. Aspergillar cardiac disease may be difficult to diagnose by current methods, does not respond to antifungal agents or cardioactive drugs, and has an extremely poor prognosis.

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Bilateral Spontaneous Renal Hemorrhage Due to Polyarteritis Nodosa

JOSEPH C. PRESTI, Jr, MD
New York, New York

PETER R. CARROLL, MD
San Francisco, California

POLYARTERITIS NODOSA is a progressive, necrotizing, inflammatory disease of the medium and small muscular arteries. The kidneys are the most common organs involved (70% to 80% of cases). Although the cause is unknown, much evidence supports an autoimmune origin, and an interesting subgroup of patients shares a history of intravenous methamphetamine abuse. The case reported here shows the importance of the aggressive medical treatment of the disorder.

Report of a Case

The patient, a 27-year-old woman with a history of intravenous methamphetamine abuse, was evaluated at an outpatient clinic for fever of several days' duration, anorexia, arthralgia, and right upper quadrant pain. The results of liver function tests were elevated: alkaline phosphatase 805 IU per liter (normal 4 to 133); aspartate aminotransferase (previously SGOT) 81 IU per liter (normal 7 to 39); the hepatitis B surface antigen (HBsAg) test was positive; and tests for the human immunodeficiency virus were negative. Ultrasonography showed a normal gallbladder and biliary tree. The patient was treated expectantly for a presumptive diagnosis of hepatitis.

Ten days later the patient was admitted to another hospital with fever and worsening upper quadrant pain. On physical examination, she had a temperature of 39.4°C (103°F) and right upper quadrant tenderness. The hematocrit was 0.30 (normal 0.36 to 0.46), leukocyte count 25×10^9 per liter (25,000 per μl; normal 3.4 to 10×10^9 per liter), but the serum creatinine value and results of a urinalysis were normal. An ultrasonogram showed a thickened gallbladder wall, and a regimen of intravenous antibiotics was begun for a presumptive diagnosis of acute cholecystitis.

Two days later, increasing abdominal and left flank pain developed, along with abdominal guarding and rebound tenderness. The hematocrit dropped to 0.21, and the patient became hypertensive. At laparotomy, 1 liter of brown ascitic fluid was removed and the liver was noted to be firm with a fibrinous exudate. The gallbladder appeared normal. Biopsy specimens were taken from the liver and enlarged mesenteric lymph nodes. The retroperitoneum was edematous.

The patient did well until the fourth postoperative day when she became acutely hypotensive and gross hematuria developed. The hematocrit was 0.08, and the serum creatinine value was 190 μmol per liter (normal 40 to 120). She was resuscitated with the administration of crystalloid and 6 units of packed erythrocytes. Computed tomography showed bilaterally enlarged kidneys with irregular, hypodense infiltrates that, by densitometric analysis, were consistent with intrarenal hemorrhage (Figure 1).

The patient was transferred to the University of California, San Francisco, Medical Center hemodynamically stable with a hematocrit of 0.28. Renal ultrasonography showed the right kidney to be 13 cm and the left kidney 20 cm long. A review of the liver and lymph node biopsy specimens showed focal necrotizing arteritis consistent with polyarteritis nodosa. The patient remained hemodynamically stable and was given corticosteroids (3 grams of methylprednisolone sodium succinate over three days) and a pulse dose of cyclophosphamide (750 mg per m²). With therapy, the leukocyte count declined quickly from 51×10^9 per liter to a nadir of 1.7×10^9 per liter at day 16. Serum creatinine values peaked at 450 μmol per liter and stabilized at 240 μmol per liter. The patient's hypertension eventually responded to medical therapy. Magnetic resonance imaging was done before discharge and showed large, bilateral perinephric fluid collections of intermediate signal intensity on T1-weighted images that increased in signal intensity on T2-weighted images—consistent with resolving perinephric hematoma (Figure 2). Twenty days after the initiation of therapy, she was discharged on a maintenance dose of corticosteroids and cyclophosphamide. A year later, the patient was taking antihypertensive medications, had a serum creatinine level of 280 μmol per liter, and had no evidence of active polyarteritis nodosa.

Comment

Polyarteritis nodosa is a necrotizing, inflammatory disease of both medium and small muscular arteries. There is no age predilection, but it is more common in men than in women. Presenting symptoms include generalized constitutional symptoms as well as organ-specific signs and symptoms. Multiorgan involvement is common, with the kidneys being the most frequently involved. Indeed, renal disease

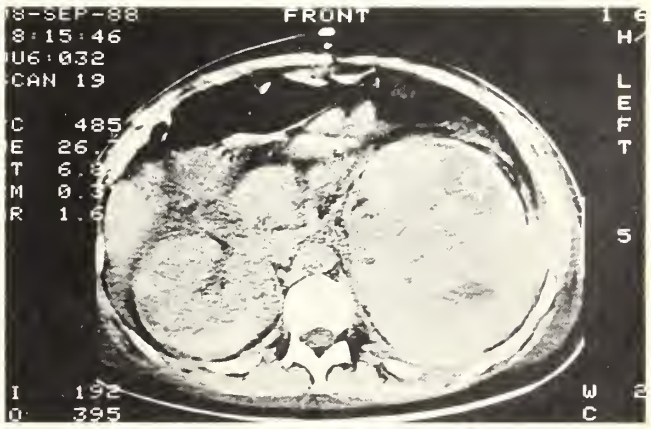

Figure 1.—A computed tomographic scan shows massive bilateral renal hemorrhage.

(Presti JC Jr, Carroll PR: Bilateral spontaneous renal hemorrhage due to polyarteritis nodosa. West J Med 1991 Nov; 155:527-528)

From the Department of Urology, University of California, San Francisco, School of Medicine. Dr Presti is now with the Memorial Sloan-Kettering Cancer Center, New York, New York.

Reprint requests to Peter R. Carroll, MD, Department of Urology, University of California, San Francisco, CA 94143-0738.

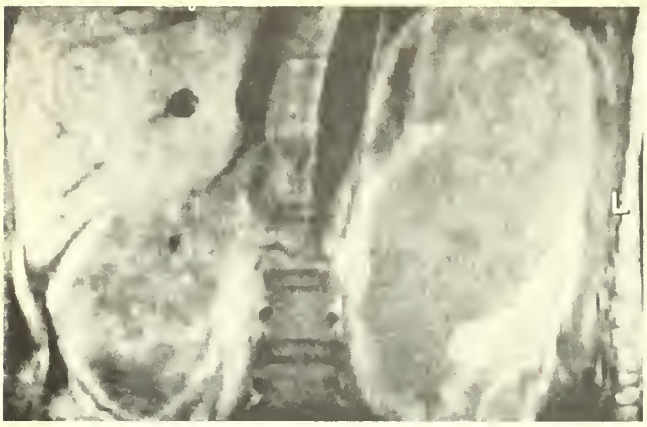

Figure 2.—A magnetic resonance image (coronal plane) 10 days after the initiation of therapy shows persistent renal enlargement and hemorrhage.

occurs in as many as 70% to 80% of patients, manifested chiefly as hematuria or proteinuria. Hypertension occurs in 50% of cases. Gastrointestinal findings due to mesenteric artery involvement are noted in 60%. Advanced disease may involve coronary arteries, resulting in myocardial infarction.[1]

Although the cause of polyarteritis nodosa is unknown, much evidence supports an autoimmune origin. As many as 30% of patients test positive for HBsAg. Hepatitis B antigen along with immunoglobulin G has been found in the walls of vessels with acute polyarteritic lesions.[2,3] An association between polyarteritis nodosa and the Australia antigen[2] as well as rheumatic fever and rheumatic heart disease[4] has been reported. A type of vasculitis that is indistinguishable from polyarteritis nodosa has been recognized in a large number of intravenous drug abusers,[5] and methamphetamine abuse appears to be a common denominator. It thus seems likely that a variety of antigens may, under appropriate circumstances, stimulate the immune system, resulting in polyarteritis nodosa.

Pathologic findings in the kidneys of patients with the disorder may be related to glomerulonephritis, arteritis of medium and small vessels, or both. Antigen-antibody complex deposition along basement membranes initiates an inflammatory response. The subsequent necrotizing reaction destroys the elastic lamina of the vessels, thus weakening the walls and resulting in aneurysm formation, thrombosis, or rupture. The arcuate and interlobular arteries are the most commonly involved renal vessels.[6,7] Aneurysm formation tends to occur at branch points and produces a characteristic "beading pattern" on angiography.[8] Renal failure remains one of the major causes of death.

Corticosteroids and cytotoxic agents are the cornerstones of medical therapy. Without treatment, half to two thirds of patients will die of renal failure or congestive heart failure within a year. With corticosteroid treatment, the five-year survival is about 40%.[1] The use of cytotoxic agents may increase survival or benefit those in whom corticosteroid therapy has failed.

Spontaneous renal hemorrhage or rupture has been reported previously in patients with polyarteritis nodosa and is typically unilateral.[9-13] In many cases, emergency surgical treatment and nephrectomy are needed. Because of the diffuse nature of the disease process, attempts at maximal renal preservation are warranted. As in the present case, aggressive medical therapy may obviate surgical intervention. Refractory cases may be successfully managed with angiographic embolization. If surgical intervention is necessary, partial nephrectomy should be attempted, if feasible, as renal failure accounts for much of the morbidity and mortality associated with the disease process.

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The Numb Chin in Metastatic Cancer

CHERYL P. HARRIS, MD
J. RICHARD BARINGER, MD
Salt Lake City, Utah

THE MENTAL NERVE is one of the terminal branches of the third (mandibular) division of cranial nerve V, the trigeminal nerve. The mandibular division exits the base of the skull at the foramen ovale and branches until it reaches the mental foramen in the horizontal ramus of the mandible. The mental nerve has many small offshoots that supply the skin of the chin and lower lip and the mucous membranes on the buccal surface of the lower lip.[1]

Many neurologic processes produce lesions of the trigeminal nerve inside the cranial vault, including vertebrobasilar vascular disease,[2] intracranial tumors,[3] and multiple sclerosis. Lesions of the mandibular division include compression by tumors, meningeal carcinomatosis, and basilar meningitis, among many other causes.

Lesions affecting solely the mental nerve are less common and generally produce more localized symptoms than involvement of the mandibular division or of the entire trigeminal nerve. Also commonly classified under the term "mental neuropathy" are lesions of the inferior alveolar nerve, from which the mental nerve branches, occurring at the mandibular foramen. In addition to the numbness of the

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From the Departments of Pathology (Dr Harris) and Neurology (Dr Baringer), University of Utah Medical Center, Salt Lake City.

Reprint requests to Cheryl P. Harris, MD, Department of Pathology, University of Utah Medical Center, 50 N Medical Dr, Salt Lake City, UT 84132.

chin and anterior teeth and gums produced by the mental nerve, involvement of the inferior alveolar nerve also produces numbness of the teeth and gums in the posterior half of the mandible.

Mental neuropathy as a manifestation of metastatic malignancy has been reported in 49 cases, some of which had not been diagnosed before the neuropathy occurred. We describe two cases of neuropathy of the mental nerve and analyze the literature regarding its occurrence in metastatic cancer.

Reports of Cases

Patient 1

The patient, a 70-year-old man, for the previous five months had had right chin and gum pain and dysesthesias. The dysesthesias began suddenly and had been constant. They extended from the midline to the vermillion border of the lower lip and were also present on the buccal surface of the right lower lip.

Four months before he was seen, a course of amoxicillin was administered: it had no effect on the symptoms. Two months before he was seen, the diagnosis of trigeminal neuralgia was considered; he was treated with gradually increasing doses of carbamazepine without effect. The use of codeine relieved the pain but did not affect the numbness.

His medical history was pertinent for severe coronary artery disease, hypertension, chronic renal insufficiency, and pancreatitis. Stage C adenocarcinoma of the prostate had been diagnosed 17 months previously and was in remission. He had a 50-pack-year history of smoking.

The findings of a general physical examination were notable for a diffusely enlarged prostate without nodules but with loss of the median raphe. On neurologic examination he had an area of hypesthesia on the right chin from the midline to the corner of the lip and extending in a vertical line inferiorly. There were no sensory alterations inside the mouth.

Radiographs of the right mandible and skull were normal. A bone scan, however, revealed multiple foci of increased activity throughout the skeleton, including the femurs; left ilium; lumbar, thoracic, and cervical spine; multiple ribs; and a lesion in the inferior ramus of the right mandible. An acid phosphatase level was 10.23 U per liter (normal 0 to 0.8), and the prostate specific antigen level was 20.2 ng per ml (normal 0 to 5).

The patient underwent bilateral orchiectomy under local anesthesia. His disease continued to progress, however, and he died six weeks after the procedure, six months after his mental nerve palsy developed.

Patient 2

The patient, a 41-year-old woman with breast adenocarcinoma and diffuse skeletal metastases, had paresthesias and numbness of the left chin. The numbness covered a discrete area from the edge of the lower lip to the angle of the jaw, not quite extending to the midline.

On a general physical examination, she had a well-healed mastectomy scar and palpable, nontender soft tissue masses spread diffusely over the scalp, with no adenopathy. A neurologic examination revealed normal masseter strength and a decreased appreciation of pinprick over the left chin from the vermillion border of the lower lip to the angle of the mandible. Unfortunately, a sensory examination inside the oral cavity was not done.

Magnetic resonance imaging (MRI) with gadolinium administration showed a loss of the normally bright fatty marrow signal on the T2-weighted image (Figure 1) in the left ascending ramus of the mandible at the level of the mandibular foramen. Infiltrating tumor was presumably replacing the marrow, causing the loss of signal. Also noted were several metastases to the scalp without invasion of the calvarium.

The patient underwent whole-brain irradiation, including the scalp and the base of the skull. When seen in clinic after the radiation therapy, the paresthesias of the chin had resolved. She has remained asymptomatic for six months.

Discussion

Nonmalignant causes of mental neuropathy have been described, including sickle cell crisis,[4-6] trauma,[7] dental manipulation,[8] mandibular osteomyelitis, mandibular atrophy,[9] and local inflammatory processes.[10] Primary tumors of the mandible, benign or malignant, also can result in mental nerve palsy,[11] as can local invasion by primary malignancy of the oral or nasal cavities, such as nasopharyngeal carcinoma.[8]

Patients with mental neuropathy present with ipsilateral dysesthesias or numbness from the chin to the vermillion border of the lower lip extending to the midline; often anesthesia of the mucosal surface of the cheek, anterior gums, or lips is noted.[1] There may be a sensation of thickening of the lip.[12] This is more localized than neuropathy of the inferior alveolar nerve, though the literature makes no distinction between the two, grouping both neuropathies under the term mental neuropathy. Compression of the inferior alveolar nerve generally occurs at the mandibular foramen, in the ascending ramus of the mandible, the location of the lesion in patient 2. Symptoms in this instance also are noted in the teeth and gums of the posterior half of the mandible. More

Figure 1.—Magnetic resonance imaging scan shows the T2-weighted image with gadolinium administration. Note the loss of the normally bright fatty marrow signal **(arrow)** in the left ascending ramus of the mandible, consistent with a bony metastasis.

TABLE 1.—*Reported Cases of Mental Neuropathy Due to Malignancy*

Source	*Primary*	*Stage of Concer With Diognosis of Mental Polsy*
Adair and Herrmann, 1946[14]	Breast	Before metastatic disease (BMD)*
	Breast	Metastatic disease present (MDP)*
Sterling et al, 1954[15]	Lung	Before metastatic disease*
Jurgens, 1954[16]	Lung	No cancer diagnosis (NCD)
Bruce and McDonald, 1954[17]	Colon	Before metastatic disease*
Castigliano and Rominger, 1954[12]	Breast	Before metastatic disease*
Blackwood, 1956[18]	Breast	Metastatic disease present
Calverley and Mohnac, 1963[7]	Lung	No cancer diagnosis
	Breast (3 cases)	Metastatic disease present
	Hodgkin's	Before metastatic disease*
Clausen and Poulsen, 1963[19]	Breast	Before metastatic disease*
	Lung	Before metastatic disease*
Nobler, 1969[1]	Multiple myeloma	Metastatic disease present
	Lymphosarcoma (5 cases)	NCD (1), BMD (1),* MDP (3)
	Hodgkin's	Metastatic disease present
	Reticulum cell sarcoma	Metastatic disease present
Horton et al, 1973[20]	Breast (4 cases)	Metastatic disease present
	Reticulum cell sarcoma	Metastatic disease present
Roistacher, 1973[21]	Breast	Before metastatic disease*
Rowe et al, 1974[22]	Reticulum cell sarcoma	Before metastatic disease*
Rohrer and Colyer, 1981[23]	Unknown primary	No cancer diagnosis
Massey et al, 1981[24]	Lymphoma (6 cases)	NCD (3), BMD (3)*
	Prostate	Before metastatic disease*
	Breast (3 cases)	Before metastatic disease*
	Unknown primary	No cancer diagnosis
	Lung	No cancer diagnosis
	Rhabdomyosarcoma	No cancer diagnosis
	Melanoma	No cancer diagnosis
	Liposarcoma	Before metastatic disease*
	Multiple myeloma	No cancer diagnosis
Banerjee and Gottschalk, 1984[25]	Squamous cell lip	Before metastatic disease*
Rotstein et al, 1988[26]	Lymphoma	Metastatic disease present
	Breast	Metastatic disease present
This report		
Patient 1	Prostate	Before metastatic disease*
Patient 2	Breast	Metastatic disease present

*Only local or regional malignancy was known at the presentation of mental neuropathy

diffuse dysesthesias occur with lesions of the mandibular branch of the trigeminal nerve, where numbness extends beyond the above borders to the preauricular area, including the tragus.[13(p224)]

Although not recognized as such, mental neuropathy from metastatic disease was first reported by Adair and Herrmann in 1946.[14] Since then, 51 cases have been reported in the English-language literature, including the current report (Table 1).[1,12,14-26] This compilation of cases does not include chin numbness from mandibular division compression by meningeal carcinomatosis, primary jaw tumors,[24] or malignant disease arising from the bone marrow of the mandible, such as leukemia[21,24] or Waldenström's macroglobulinemia.[27]

The two most frequently described metastatic causes of neuropathy of the mental nerve are compression at the mental foramen by regional lymphadenopathy[1] and that by metastases to the lower mandibular ramus. Metastases to the skeletal system by carcinomas are common, but involvement of the upper and lower jaws is infrequently recognized.[28] It has been thought that the infrequency of observed metastasis to the jaws is due to a lack of symptoms, a failure to include the mandible and maxilla in skeletal surveys, and an inability to examine the jaws fully at autopsy.[23]

Various authors have emphasized that jaw metastases are often the first signs of malignancy.[12,19,23] In a 1963 study by Clausen and Poulsen,[19] 97 cases of carcinoma metastatic to the jaw were examined: the most common primary sites included breast (31%), lung (18%), kidney (15%), thyroid (6%), prostate (6%), and colon (6%), and melanoma (5%). Other primary tumors metastasizing to the jaws less frequently include ovary, testis, salivary gland, and gastric adenocarcinoma and sarcoma.[12]

Signs and symptoms of jaw metastases other than mental neuropathy include pain, swelling, the loosening of teeth, and pathologic fracture.[23]

In an analysis of the 51 cases of mental neuropathy reported, 70% were presumed to be from metastases to the mandible, 10% were due to regional lymphadenopathy, and in 18% of cases, the cause was not clear. An additional case showed metastases to the gingiva with no bony changes.[15]

Many of the cases were not proved either radiologically or pathologically but were presumed metastatic in the presence of known metastatic disease. Massey and co-workers considered a response to radiotherapy to the mandible presumptive evidence of metastatic tumor.[24]

Plain radiographs of the mandible showed metastatic tumor in only 46% of the cases; in the other cases, the radiographs were not done or were normal. Computed tomography or MRI of the mandible was not reported in these cases before this report.

Of the 51 cases of mental neuropathy summarized here, the primary malignant neoplasms were breast (35%), lymphoma (20%), lymphosarcoma (16%), lung (10%), myeloma

(4%), prostate (4%), and carcinoma of unknown primary (4%). The other primary sites were present in only single cases.

Metastasis to the jaw and neuropathy of the mental nerve have previously been noted to be symptoms of rapidly progressive and soon fatal disease.[1-19] Our review confirms this observation: the average survival after mental neuropathy was diagnosed was only 5.4 months, the range being from 2 weeks to 28 months; information was not available for ten patients.

The most important aspect of the diagnosis of mental neuropathy is the number of cases in which it is the presenting symptom of an undiagnosed underlying cancer. In 12 of the patients (24%), there was no recognized malignant process before the "numb chin." In 20 patients (39%), malignant tumor was either regional or in remission when the mental neuropathy appeared. This has important implications for the treatment of the malignant disease; our first patient underwent further therapy based on the knowledge that his prostate carcinoma, previously in remission, was now widely metastatic.

Considering this aspect, patients presenting with a neuropathy of the mental nerve with no history of cancer should have plain radiographs of the mandible and a skeletal survey or bone scan to evaluate for other osseous lesions. If these studies are normal, MRI with gadolinium administration appears to be a sensitive method for diagnosis.

Also required is a search for a primary neoplasm encompassing the most common sites of breast, lung, tumors of the lymphoreticular system, myeloma, and prostate carcinomas.

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Massive Splenic Infarction in Doubly Abnormal Heterozygous Sickling Disorders

A New Complication of Acute Splenic Sequestration Syndrome

ROY A. BERRY, MD
ELIZABETH A. ODUMAKINDE, MD
JERRY P. LEWIS, MD
Sacramento, California

ACUTE SPLENIC SEQUESTRATION syndrome and acute splenic infarction are sequelae of sickle hemoglobin disorders and occur in children with sickle cell disease (hemoglobin [Hb] SS) and adults with Hb SC disease or hemoglobin S-β-thalassemia. Exposure to high altitude while mountain traveling or flying in an unpressurized plane are well-known precipitating events. Prompt transfusion is essential for the management of acute splenic sequestration syndrome; symptomatic treatment is usually effective in the management of acute splenic infarction.

Acute, massive, and complete splenic infarction is rare in adults and when diagnosed is usually seen in association with doubly heterozygous sickling disorders. We have recently seen two patients with complete splenic infarction and have identified two other cases from the literature. The patients had doubly abnormal heterozygous sickling disorders and no exposure to high altitude. In three patients, massive splenic infarction was preceded by well-documented acute splenic sequestration syndrome. In the fourth case, acute splenic sequestration syndrome likely preceded complete splenic infarction. All patients required splenectomy.

Reports of Cases

Patient 1

The patient, a 22-year-old African-American man with hemoglobin S-β-thalassemia, was admitted with lower extremity discomfort and ill-defined lower abdominal pain typical of his previous painful crises. His leukocyte count was 8.7×10^9 per liter (8,700 per μl), and his spleen was not palpable. On day 3 he suddenly became obtunded and was

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From the Department of Internal Medicine (Drs Berry, Odumakinde, and Lewis) and the Division of Hematology and Oncology (Drs Odumakinde and Lewis), Department of Pathology, University of California, Davis, Medical Center, Sacramento.

Reprint requests to Jerry P. Lewis, MD, Division of Hematology and Oncology, UCD Medical Center, 4501 X St, Sacramento, CA 95817.

transiently hypotensive. Serial electrocardiograms, coupled with cardiac enzyme changes, confirmed a subendocardial infarction. On ultrasonogram, his spleen was found to be enlarged, and it eventually became palpable as his hemoglobin fell from 143 (14.3) to 87 grams per liter (8.7 grams per dl). An exchange transfusion was carried out and a scan of leukocytes labeled with indium 111 showed a complete absence of splenic uptake. The patient's condition deteriorated with his temperature rising to 41.5°C, his left upper quadrant pain increasing, and his leukocyte count rising to 37.9×10^9 per liter. Because conservative management had failed, a splenectomy was done on day 19. The spleen weighed 950 grams and was totally infarcted. The patient's recovery was prompt and complete. The non-Q wave myocardial infarct occurred at the time of splenic sequestration and may have contributed to the clinical state.

Patient 2

The patient, a 29-year-old African-American man with Hb SC disease, was admitted with mild sternal and moderate to severe sacral and left leg pain typical of his previous sickle crises. His leukocyte count was 11.9×10^9 per liter, and his spleen was not palpable. The chest x-ray film showed a left lower lobe infiltrate, and blood gas values were within normal limits. Over the next several days, his hematocrit dropped from 0.36 to 0.23 and his spleen enlarged. The patient became dyspneic and febrile, and a mild productive cough developed. He was thought to have acute splenic sequestration syndrome with pneumonia. He was transfused, placed on a regimen of antibiotics, and his condition improved rapidly. He was discharged on day 5 with a hematocrit of 0.38, only to be readmitted a day later with a temperature of 38.2°C, left upper quadrant abdominal pain, and left shoulder pain. His leukocyte count was 29.7×10^9 per liter, and his hematocrit remained stable at the concentration achieved following his exchange transfusion.

On ultrasonogram, the spleen showed numerous intrasplenic cystic areas, and a liver-spleen scan with technetium Tc 99m sulfur colloid showed complete absence of splenic uptake. The patient deteriorated clinically and was taken to surgery where a 1,250-gram spleen was removed that was totally infarcted. After the operation, he rapidly improved. Throughout his second hospital admission, Howell-Jolly bodies were noted on his peripheral blood smear. They were not seen on a retrospective review of peripheral smears from his earlier hospital admission.

Discussion

Two cases smiliar to ours have been reported.[1,2] Sears and Udden reported the case of a 29-year-old African-American man with Hb SC disease who presented with typical painful crisis, a barely palpable spleen, and mild left upper quadrant abdominal tenderness. By the ninth day, the patient was severely obtunded and had hypotension, tachycardia, and a fever (40.2°C [104.4°F]). The spleen had enlarged to 8 cm below the left costal margin, and his hematocrit had dropped from 0.43 to 0.12. Nucleated erythrocytes were noted on the peripheral blood smear. On hospital day 23, because of continued deterioration, a splenectomy was done. The spleen weighed 1,870 grams and showed multiple and extensive areas of recent infarction and evidence of acute splenic sequestration syndrome.

Fishbone and co-workers reported the case of a 25-year-old African-American woman with Hb SC disease who presented with pronounced left upper quadrant abdominal pain, chills, cough, and splenomegaly.[2] Her hemoglobin level was 100 grams per liter, leukocyte count 19.5×10^9 per liter, and numerous Howell-Jolly bodies were noted on her peripheral blood smear. The patient was transfused without relief of her symptoms, and a celiac arteriogram showed splenomegaly with a marked delay in splenic blood flow. On splenectomy, the spleen weighed 753 grams and showed extensive hemorrhagic infarction with thrombosis. In this particular patient, there were no previous records to demonstrate the presence or absence of splenomegaly or a recent fall in hemoglobin. Nevertheless, after the operation the hemoglobin level rose to above 130 grams per liter, suggesting that this was the patient's usual level.

Several authors have implied a possible relationship between the acute splenic sequestration syndrome and massive splenic infarction.[1,3-5] Acute splenic sequestration is mimicked by ligation of the splenic vein in dogs and could be explained in sickling disorders by the sickling of erythrocytes in efferent channels of the spleen, which sets off a chain reaction that progressively involves more afferent channels until the entire spleen is infarcted. Indeed, studies of blood flow through the spleen during periods of acute splenic sequestration verify that flow is greatly retarded or nonexistent.[1] What has been lacking to convincingly relate the two complications of sickle cell disorders has been documentation of cases of patients with sickle hemoglobinopathies in whom the clinical features of acute splenic sequestration syndrome developed, followed by clinical deterioration, with splenectomy showing complete or massive splenic infarction. In this report of two cases, along with the cited cases, we document this relationship. Two cases occurred in patients with Hb SC disease, and two occurred in patients with Hb S–β-thalassemia. Each appeared to have had acute splenic sequestration syndrome terminating in massive and complete splenic infarction requiring splenectomy.

Acute splenic sequestration syndrome unresponsive to transfusion therapy may result in acute splenic infarction requiring a splenectomy. If conservative management with transfusions does not result in improved clinical states of patients with doubly heterozygous sickle hemoglobinopathies, complete or massive splenic infarction should be considered. Because diagnostic studies of splenic blood flow do not distinguish between the splenic sequestration syndrome and massive splenic infarction, the decision to operate must be based on clinical findings. Patients with doubly heterozygous sickle hemoglobinopathies in whom acute splenic sequestration syndrome develops who continue to deteriorate clinically after transfusions should be considered as candidates for splenectomy for possible massive splenic infarction.

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Commentary

Managed-Care Plans
Their Future Under National Health Insurance

THOMAS P. WEIL, PhD, *Asheville, North Carolina*

The nation's health maintenance organizations, preferred-provider organizations, independent practice associations, and similar managed-care efforts are not well positioned to take a leadership role in a nationwide universal access or national health insurance plan. They—with the possible exception of some large staff and group health maintenance organizations—have been unable to show uniformly that they can contain costs, provide better access or higher quality of care, and achieve greater patient satisfaction than fee-for-service endeavors. As the United States pursues universal access as a step toward national health insurance, the managed-care plans will continue to increase their numbers of subscribers. They will not, however, be able to enroll large numbers of the young, low-income employees and their dependents who account for most of the 63 million people uninsured sometime during each year. Under national health insurance, there might be an option for some health maintenance organizations to negotiate capitated payments. The vast majority of the nation's physicians, however, will reluctantly embrace a centrally managed fee-for-service approach rather than a salary or capitated reimbursement method, leaving only a trace of the competitive managed-care plan theme in a future, primarily monolithic, national health care system.

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Access to needed services, high-quality patient care, value for the dollars expended, and patient satisfaction are considered major hallmarks of an effective managed-care plan. These are most popular in the West, where more than 55% of the employees who are insured through their employers are enrolled in health maintenance organizations (HMOs) or preferred-provider organizations (PPOs).[1] In fact, one proposed option for national health insurance is to have all payments made on a capitated basis to closed-panel plans like HMOs, which in turn would organize the delivery of health care services for their subscribers.[2]

Of the many changes that now affect our health care delivery system, perhaps none is of greater consequence than the "managed-care" revolution—the rapid growth during the 1980s of HMOs, PPOs, independent practice associations (IPAs), hybrid structures, and even fee-for-service approaches that include prospective utilization review and provider-selection standards. While this great diversity in the delivery of health care services provides a natural experiment to evaluate the efficacy of managed-care plans, universal access and national health insurance have become major domestic issues.

Recent opinion surveys indicate that nearly three out of four Americans are in favor of national health insurance,[3] and an increasing number of provider groups, including the American Medical Association[4] (AMA) and the Health Insurance Association of America (HIAA), favor universal access, if not universal insurance. The question therefore arises whether or not managed-care plans as we know them will play an increasingly important role in the future organization and financing of physicians' services that begins with universal access and leads eventually to a national health insurance plan.

Managed Care—A Model for National Health Insurance?

The early advocates of prepaid group practice[5] had high expectations for the ability of managed-care or similar plans to contain costs, improve access, promote quality care, and ensure patient satisfaction—key elements in their long-term leadership role in a universal access or national health insurance plan.

Utilization and Cost

In an early study (1961-1974) of HMO versus fee-for-service performance, the managed-care plans provided a one-time cost saving by reducing hospital use.[6] The premiums for HMOs then rose on an annual basis just as rapidly as the fee-for-service plans. Later (1972-1982), when the effect of HMOs was compared with regulatory approaches in the nation's 25 largest standard metropolitan statistical areas (with controls for environmental conditions in each of these markets),[7] neither the managed-care-type competitive nor the regulatory model substantially reduced overall hospital costs.

Despite these early findings, it was expected that costs could be contained in regional or local medical care systems with a high percentage of HMO enrollees, such as Hawaii; Rochester, New York; and Minneapolis/St Paul, Minnesota. In none of the three sites studied, however, was there a demonstrable connection between reducing hospital use and HMO competition. Instead, reductions were "in each case attributable to other factors—including biases in data, long-term trends predating HMOs, indirect effects of policy changes, and other forms of competition."[8(p625)] Competition from HMOs did not have the anticipated effects on hospitals until relatively recently as it neither directly addressed the

From the Bedford Health Associates, Asheville, North Carolina.
Reprint requests to Thomas P. Weil, PhD, President, Bedford Health Associates, BB&T Building, Suite 1019, Asheville, NC 28801.

ABBREVIATIONS USED IN TEXT

AMA = American Medical Association
HIAA = Health Insurance Association of America
HMO = health maintenance organization
IPA = independent practice association
PPO = preferred-provider organization

payment issue for inpatient care nor encompassed the range of forces that increase competition and foster cost-consciousness in the medical care arena.[9,10]

Compared with similar fee-for-service practices, more recent studies indicate that HMOs organized as staff and group practices have successfully reduced the rate of hospital admissions and the overall expenditures for physician services by 30% to 40% and for hospital services by 10% to 40%.[11,12] To attain these utilization and cost reductions, however, physicians have generally been paid on a salary or capitated basis and hospitals have been encouraged to accept lower reimbursement to ensure increased market share. In contrast, IPAs or foundations for medical care that pay independent physicians on a fee-for-service basis have not proved to be less expensive than pure fee-for-service practices, having traded lower inpatient for higher ambulatory use rates.[13-15] The overall impression is that staff and group HMOs might provide high-quality, lower-cost care than IPAs or fee-for-service plans. Additional longitudinal studies are needed, however, to compare matched patient populations and to evaluate patient satisfaction and the quality of care provided with the decreased hospital use patterns often noted in HMOs.

Access to Care

To contain utilization and ensure operating surpluses, both traditional fee-for-service and managed-care plans practice patient skimming, or the selective enrollment of only healthy groups or persons.[16-20] A possible problem is that managed-care plans might refuse to enroll those high-risk, high-cost uninsured persons who could clinically and fiscally profit the most.

Another way in which HMOs reduce access to care is by fostering the likelihood that unethical behavior on the part of physicians could increase when there is no trusted and impartial "gatekeeper" acting on behalf of patients.[21] Of the HMOs in one survey, 40% required primary physicians to cover outpatient laboratory costs out of their capitated payments.[22] Some plans pay primary physicians at the end of each year as much as 50% of the unspent funds allocated to hospital care, thereby providing a strong incentive to avoid inpatient use. Bodenheimer concluded that

> this type of direct personal financial incentive—in which payment for the basic referral tools of the primary physician is deducted from that physician's own income—has great potential for abuse by underdiagnosis and undertreatment.[23]

Quality of Care

Although physicians have traditionally focused on high-quality patient care, given the incentive for undertreatment with HMOs, is there any detectable difference in the quality of care provided by fee-for-service practices compared with capitated plans? Although HMOs have been criticized for expending insufficient resources on preventive services and providing inadequate access to care (particularly to lower-income patients), there is evidence that established HMOs deserve high marks on the overall quality of care rendered.[24,25] One of the difficulties in generalizing about the quality of care provided by managed-care plans is that the values and performance of the respected capitated plans differ greatly from some of the for-profit Medicaid and Medicare HMOs, for example, that sprang up particularly in California and Florida during the 1970s and 1980s.

Patient Satisfaction

Enrollees are generally highly satisfied with PPOs but less pleased with HMOs.[26] They tend to rate physicians' competence and willingness to discuss problems lower among HMOs than those in fee-for-service plans. It has not been determined whether this perception reflects real differences in competence rather than the amount of time physicians spend with their patients. The interpersonal aspects of the physician-patient encounter may suffer in a managed-care setting because of time pressures, without diminishing either the quality or the outcome of treatment.

In brief, the earlier enthusiasm for HMOs is waning, as shown by the current slowed growth in enrollment. The early financial statements of most plans showed that they needed to select more desirable risks, further cut utilization, or reduce the cost per unit of service, strategies that could then adversely affect their public image and the quality of care provided. Consumers who place a high priority on a free choice of provider and who will only choose an HMO if it is to their distinct fiscal advantage may limit increases in HMO enrollment.

If managed-care plans were the answer to the nation's health care problems relating to costs, access to care, quality, and patient satisfaction, HMOs would already have been mandated by at least one highly regulated state; in fact, these plans to date have fallen short of the results anticipated by some of their early advocates. This then leads to the question: Will managed-care plans have a major role in either universal access or a national health insurance plan?

Universal Access as the First Step

There are almost insurmountable problems to resolve and many compromises to be struck, but universal access will be enacted in more states soon and then nationally. This is largely because the continued rationing of care on the basis of a patient's insurance coverage or ability to pay is no longer acceptable to an increasing number of Americans.

There are several reasons why universal access appeals to elected officials, key provider groups, business leaders, and the uninsured.[27] First, even though it is likely that those previously uninsured will receive only limited physician and hospital benefits, universal access can be packaged by public officials as a monumental step toward meeting the nation's current health care crisis. Second, a universal access plan can be so designed that it gains the support of managed-care plans and other providers by allaying the fear of a monolithic—that is, all-government—system of funding and control. A universal access bill could be so designed that there would be relatively few changes in the current pluralistic delivery of health care services.

Third, with a pluralistic financing and administrative approach, there is a reasonable chance that a higher percentage of the nation's gross national product will be spent for health care services, giving managed-care plans and other providers

a larger pool of dollars. Fourth, as a result of state, federal, and private sector fiscal constraints, the extent of the basic benefits mandated for the uninsured will, in all likelihood, fall short of the more comprehensive coverage considered necessary. The managed-care plans could then opt not to seek new enrollees or selectively enroll additional subscribers, many of whom would be young, low-income wage earners and their dependents. Finally, and possibly more critical at this time, private and public sources will be more willing to share the additional costs of a universal access plan to meet a now well-publicized social need because they perceive it to be more affordable than national health insurance.

With mandated universal access and a projected increase in total health care dollars available, those managed-care plans that have proved most effective in controlling utilization and cost per unit of service and have a reputation for high-quality care for the premium expended will continue to prosper. Can these plans expect the same outcome under national health insurance?

National Health Insurance as the Second Step

Universal access, for the reasons just detailed, will be a major step (following Medicare, Medicaid, and others) toward a national health insurance plan. Some of the same problems, however, that plague managed-care plans could cause this approach to fail under a more regulated, bureaucratic environment.

Eligibility

Under universal access, an average of 33 million—or, at a given point during the year, as many as 63 million—additional Americans would need to be provided with some basic physician and hospital benefits. This large, heterogeneous, newly insured population will be primarily young, low-wage earners who frequently exhibit transitory employment and dependency relationship patterns. This suggests that universal access could fail because of a built-in difficulty in defining eligibility and determining which of the three major potential sources of health care benefits—the employer's coverage, the state-subsidized health insurance risk pool,[28] or the expanded state Medicaid program—should bear the costs.

Under universal access, the managed-care plans might be able to increase the number of enrollees by only 3 to 4 million subscribers (say, 10% of those currently uninsured) because most HMOs are not set up to meet the needs of Medicaid recipients or those covered by state risk pools.[29] Moreover, few employers in service industries (excluding those related to health care), in retail sales, and in agriculture—which account for most of the uninsured—will be able to afford to offer HMO coverage. Rather than 1,500 or more competing companies nationwide providing health insurance coverage, or enrolling members and then constantly changing insurer or arguing with a carrier about which benefits are covered, many people would simply prefer being eligible for a card that guarantees universal access and compulsory health insurance benefits to every member of the family. The rationale for not enacting national health insurance now or for the past half century is documented extensively elsewhere.[2,30-33]

Benefits

To keep universal access affordable and ensure that it does not compete with existing health insurance contracts, basic physician and hospital benefits will be limited. In fact, for managed-care plans to enroll many of the currently uninsured, they might organize coverage for most of these new subscribers through low-cost, low-overhead "Medicaid mills." The result could well be rationing, patient dissatisfaction, low quality of care, forced disenrollment of high-cost patients, and a deteriorating public image for HMOs.

If the nation's 25-year-old Medicaid program and the state risk pools are any example, universal access will fail because it will not be able to provide the 33 million persons who were previously uninsured the care they thought had been promised to them, thereby setting the stage for the passage (on an incremental basis) of national health insurance. With the potential for more broadly mandated benefits, the managed-care plans are in a better position to provide the comprehensive benefits envisioned under national health insurance, rather than universal access with its limited physician and hospital benefits.

Containing Costs

Although managed-care plans may not have had sufficient time to demonstrate cost-containing capabilities, their performance to date suggests that competitive market forces cannot contain the nation's future health care expenditures. The Medicare prospective payment system and the diagnosis-related groups, which have been described as a "pure type of regulatory intervention, despite its being occasionally clothed in market rhetoric,"[34] are the major successes of the competitive ideology of the Reagan-Bush era.

On a larger scale, in the AMA, HIAA, and some of the other universal access proposals, approaches like the current pluralistic system (multiple versus single payer), no mandatory assignment (acceptance of the assigned fee as total payment), and cost shifting from the public to the private sectors could remain the nation's predominant reimbursement methods. These issues are central to any discussion of the probable fiscal failure of universal access and the implementation of any national health insurance program.

American health care has evolved into a complex prepayment system of multiple organizations, not-for-profit and commercial carriers competing for enrollees, and various public programs covering the more onerous risks. A national health insurance plan could choose to mandate premium payments to HMOs and other carriers, thereby keeping the current multiple-payer system intact and able to continue with current administrative costs. An alternative is a single payer of health care costs at the state or federal level. Such a payer would collect taxes, Social Security contributions, and employer-employee premiums in one fund and use these monies to pay health care professionals through newly established state health services commissions.

The perceived difficulty in financing universal access without universal insurance is related at least in part to the experience that the United States, with multiple payers of health care and allowable extra billing, has suffered a relentless rise in health care costs. By comparison, Canada, with a single payer and thus no possibility of cost shifting and with mandatory assignment, has had more success controlling costs while providing universal access to care.[34(p571)] Japan, Great Britain, and other Western European countries have done much the same.[23] In these nations, the overall quality of care, as shown in gross measures of health status, equals or exceeds that of the United States. Moreover, France, West

Germany, and the Netherlands, with health care systems that more closely approximate the single-payer approach, have also been better able to control costs without adversely affecting quality of care.

On a more specific level, the new resource-based relative-value-scale Medicare fee schedule (being phased in over a five-year period starting in 1992) will be under attack by hospital-based physicians and many medical and surgical subspecialists, even though it will initially have only modest adverse effects on most of their incomes. Under national health insurance, it is unlikely that physicians would be paid an annual salary adjusted for specialty, experience, location, and other factors or on a capitated basis such as the one used by the British National Health Service. As a result, the Medicare relative-value or resource-based approach would become a critical historical precedent because it will be the linchpin in the reimbursement method with universal access and, later, universal insurance.

Under these circumstances, for physicians to support a national health insurance plan, they will have to be reimbursed under a universal and comprehensive public program according to a fee-for-service schedule. The fee schedule would be based on the then-existing Medicare and modified and expanded relative-value units, negotiated periodically between professional associations and state health services commissions. In the early years under national health insurance, physicians will probably be allowed to bill for extras, but this provision will be eliminated, once the universal insurance principle has been firmly established, to reduce the nation's overall health care expenditures and to portray a more egalitarian image for the plan.

A possible option available to then-existing managed-care plans would be to negotiate capitated rates with the state health services commissions. Under national health insurance, can managed-care plans provide comprehensive care at lower cost to patients or the state agency? Can HMOs provide higher quality than fee-for-service care? Can the HMOs provide the sort of patient-physician relationship that would enable this form of organization to become the dominant pattern across the nation? The evidence presented earlier suggests that large staff and group HMOs, which for the most part are also highly capitalized and leveraged, might have difficulty in successfully negotiating agreements with state health services commissions. Also, it is difficult to imagine that physicians with few of their patients eligible for HMOs, PPOs, IPAs, or similar arrangements will choose a capitated payment when fee-for-service is the prevailing payment method. This could well signal the death knell for almost all managed-care organizations under national health insurance.

Administering the Programs

As the dialogue about universal access and national health insurance continues, the Woolhandler-Himmelstein estimate of a $62-billion (1989) savings by virtue of a monolithic rather than pluralistic administration of a health insurance plan will attract much more interest.[35] As we look toward the possible implementation of a plan of universal access without compulsory insurance, we can also expect the probable establishment of new state health services commissions to administer Medicaid, risk pools for the uninsured, and other related functions. There is the obvious concern about federal and state governments' abilities to recruit staffs of qualified public servants who will be able to engender the level of trust among physicians, hospitals, and other providers needed to effectively and efficiently implement universal access and, eventually, compulsory health insurance.

Most managed-care plans to date have been unable to uniformly show that they can contain costs, provide better access, provide better health care, and ensure more patient satisfaction than fee-for-service arrangements. As a result, they are not particularly attractive candidates for long-term leadership roles in a universal access or national health insurance plan. Moreover, managed-care plans are not well positioned to deliver care to the approximately 30 million young, low-wage earners and their dependents who will have basic physician and hospital benefits under a new universal access plan. Later, when a national health insurance plan is enacted with a fee-for-service payment plan as the predominant pattern, physicians will embrace that rather than reimbursement on a capitated basis. Based on the history of their inability to contain costs in a procompetitive era and the uncomfortable conceptual fit with the far more regulatory and bureaucratic approach under national health insurance, it is difficult to imagine that more than a few of the existing managed-care plans will play a key role in providing health care services in the next century.

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DOCTOR'S WIFE

Feeling her bones
the way he does
helps him to do his job,
and he says so frankly
because he knows you know
it's up to him to write
the story of other women's lives.

He can talk for hours
about veins and arteries
and you listen,
remembering it's his profession
and not to be taken personally,
that each night his hands,
busy as ever,

will prove
that loving you
is what he has been doing
all day long.

CONSTANCE PULTZ©
Charleston, South Carolina

Commentary

Physician, Heal Thy Planet

WILLIAM B. STEWART, MD, *San Francisco, California*

In developing a theory of the earth as a living organism, James Lovelock, in his book *The Ages of Gaia: A Biography of Our Living Earth*, suggests the need for a new profession—planetary medicine.[1] He credits James Hutton, the 18th-century physician and geologist, with first introducing the idea of planetary physiology. Is it not, after all, the health of the planet that matters most, not the health of one species among millions? And is not the survival of the earth's many life forms intimately entwined?

We have been reminded again and again by philosophers of both Eastern and Western orientation that our attitude toward the world has often led us to paths excessively anthropocentric. Yet we remain oblivious to the consequences of our actions, consequences that often distance us from our natural world. The insightful Chief Seattle of the Duwamish (Suquamish) tribe poignantly described the connection between humans and the earth. In a letter to President Franklin Pierce in 1854, marking the transfer of Indian lands to the United States government, he wrote,

> The President in Washington sends word he wishes to buy our land. But how can you buy or sell the sky? The warmth of the land? The idea is strange to us. If we do not own the freshness of the air and the sparkle of the water, how can you buy them? . . . This we know. The Earth does not belong to man. Man belongs to the Earth. This we know. All things are connected like the blood which unites all in one family. Will you teach your children what we have taught our children? That the Earth is our mother? Whatever befalls the Earth befalls the sons of the Earth. Man did not weave the web of life, he is merely a strand in it. Whatever he does to the web, he does to himself . . . (reprinted in *Solstice*, December-January 1989, issue 34, p 72).

Considering the pace of human population growth, industrial and technologic "progress," and our exploitation and consumption of the earth's resources, the words of Chief Seattle seem prophetic and timely, for our actions have served to "soil our nest." Now we are faced with many examples of environmental degradation that directly affects human health. The media daily remind us of the implications of global warming, ozone depletion, air pollution, water contamination, topsoil erosion, rain forest destruction, species extinction, human overpopulation, waste disposal, threat of nuclear disaster—the list seems endless. The tabulation of our environmental problems is analogous to the table of contents of a medical textbook describing human disease. Congenital deformities, infection and infestations, degenerative changes, fluid and electrolyte imbalances, nutritional deficiencies, respiratory distress, mental illness, and cancers plague our bodies like the maladies of our environment. The effect of our presence and actions on the health of the planet is difficult to deny.

We must recognize our intimate relationship to the earth and our responsibility in creating the planet's health. Although our scientific training and reliance on rational proofs and empirical data can often separate us from wisdom otherwise gained, scientific inquiry has taught us about our elemental relationship with our world. We know that our atomic structure—protons, neutrons, electrons—is identical to that of all organic and inorganic substances. The chemical components of carbon, hydrogen, and oxygen are the same in humans as in "nature." From the "Big Bang" on, the scientific story of evolution confirms the common origin of all that is present on the planet. Nor are the similarities merely anatomic or microscopic. Physiologic relationships further define our interrelatedness. The proportion of water in our bodies is the same as on the earth's surface. The concentration of salt in the oceans is similar to that in human blood. The proportion of oxygen in the atmosphere allows aerobic reactions without uncontrollable combustion. The universe is expanding fast enough so the force of gravity does not draw all back to implode but slowly enough so that we do not fly off unrestrained into distant space. The microscopic and macroscopic relationships between humans and the natural world and the maintenance of the delicate life-sustaining proportions remind us of the intimate interconnectedness and dependency between humans and the planet. They remind us also of the possibility of looking at the earth as a whole, as if it were a living organism.

Before the advent of contemporary scientific thinking, many peoples gained the wisdom to live in harmony with the earth. Our 20th-century population explosion and life-styles have separated us from the kind of relationships our forebears had with their habitats. Nonetheless, we need to accept that all of us need to be as fully a part of our surroundings as are the Native Americans, Eskimos, tribes of Africa, nomads of the Sinai, herders of Tibet, and others who live close to the land and sea. Our health and our planet's survival may be in jeopardy until we can care for our environment with more compassion.

With the recognition of our planetary heritage and interdependency, we can begin to accept the responsibility to heal the planet by first healing ourselves. As a journey of a thousand miles begins with one step, so, too, must our practice of planetary medicine begin with the creation of human health in the fullest sense. Health creation includes not only treating diseased states but also establishing physical, mental, emotional, spiritual, and societal well-being. It acknowledges the importance and balance of nutrition, work and play, rest and relaxation, as part of "wellness." It is a practice that recognizes the effect of our behavior on our surroundings and how environmental influences affect our health. It is an approach that learns not only from science and technology but also from the wisdom and traditions of the past and accepts ways of knowing and understanding that are not always "rational."

(Stewart WB: Physician, heal thy planet. West J Med 1991 Nov; 155:538-539)

Dr Stewart is the Executive Director, Program in Medicine and Philosophy, California Pacific Medical Center, San Francisco, and is in private practice.
Reprint requests to William B. Stewart, MD, 2100 Webster St, Suite 214, San Francisco, CA 94115.

It is a practice that is mindful of the brain and the heart, the earthly and the astral, the minute and the monumental.

As with the practice of species-specific medicine, the practice of planetary medicine requires careful diagnoses based on an accurate assessment of signs and symptoms and pertinent laboratory studies. Treatment ranges from dietary adjustments and behavior modifications to extensive surgical procedures. Organ transplants save lives just as recycling preserves precious and finite resources. While each of us must recognize the web of life in our own way, our practices must reflect a planetary view, acknowledging that our health is intimately linked to the survival of the planet. Our needs must be seen in the context of the needs of the planet, not just for today but for the future. We must accept our humble position in the global hierarchy. Resisting the temptation to be overwhelmed by the enormity of global problems, we must demonstrate an individual resolve to the "rightness" of each of our actions.

"Whatever befalls the Earth befalls the sons of the Earth" (Chief Seattle, *Solstice*, 1989; [34]: 72). We are tenants, not landlords, of this earth, and we must all practice planetary medicine in the living of our lives.

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OLDER BROTHER

August afternoons when the sky darkened with storms
we'd climb the old silver maple
high as its limbs could hold us
and ride that wind that rocked the wren house
and turned grape leaves to their white undersides

down on the arbor. He'd lean into it
like a prow, his hair cowlicked back
seeming to stare at something beyond
our hills of sheep and junk yards, unflinching
even when rain spattered his glasses.

That's how I think he looks now,
walking on silent shoes through the wards
delivering news to families too stunned to question
the voice that pronounces so surely
still birth or the names of cancers.

But I wonder if there is ever a father,
a mill worker with large, blackened fists
who grabs the narrow lapels of his lab coat
and pounds on my brother's chest,
demanding that he take it back.

JULIA KASDORF
Brooklyn, New York

Editorials

There's a Long, Long Trail A-winding . . .

WOMEN HAVE BROUGHT special skills, outlooks, and, yes, intuition to the medical profession and have enriched it. We have been sought out by many patients, welcomed by others, and at least tolerated by the remainder. We have been graced by mentors and colleagues who live by fairness and honor talent where they find it.

The first woman physician trained in the United States, Elizabeth Blackwell, was admitted to Geneva Medical College in 1847, despite opposition from the faculty, who delegated the decision to her rowdy prospective classmates. The class voted unanimously in her favor after the one "nay" voter was beaten into submission. Her attendance at classes brought order to chaos despite the tumultuous admissions process. "The sudden transformation of this class from a band of lawless desperadoes to gentlemen, by the mere presence of a lady, proved to be permanent in its effect."[1(pp65-66)] It seemed a promising beginning, but the path ahead was to be marked by controversy, restrictions, and unpleasant incidents. Indeed, Elizabeth Blackwell's own sister was denied admission to Geneva despite Elizabeth's fine record because the faculty did not wish to set a precedent. In 1850, the Harvard Medical School admitted a woman student, along with three African Americans, but all were forced to withdraw after student riots; women were not admitted to Harvard again until 1945. In 1919, when the distinguished occupational medicine specialist, Alice Hamilton, became the first woman physician faculty member at the Harvard Medical School, conditions were attached that seem almost unbelievable. This woman, adjudged to be sufficiently outstanding to be given a faculty appointment, could not join in academic processions; could not be a member of the faculty club; could not exercise the faculty option for season football tickets!

It has not been an easy road. Women physicians have endured comments, jokes, prods, and worse. Some have been passed over, ignored, dismissed. My internship in the 1960s was marred when I was slapped in the face by a professor because I could not answer his question. I did not report the incident. It didn't occur to me to do so. Even today, as women contend with covert or overt discrimination, most do not or cannot speak out.

Data continue to confirm women's slower promotion in academic faculty ranks compared to men.[2] Although women physicians work 8% fewer hours per week than men, women earn about 40% less than men.[3] Leaders inside and outside medical schools have been slow or unwilling to set standards to make sexist barbs and practices wholly unacceptable. Professional organizations seem to have an overweening pride about the rather few women who belong and the very few who lead.

How have women physicians weathered tough times and unfairness? We have had support from family, friends, faculty, and colleagues. We haven't complained much. Complaining wouldn't be seemly; it would also be a career-limiting activity. We have worked extraordinarily hard, have deliberately chosen specialty roads less travelled or more predictable in order to avoid competition or haphazard schedules. We have tempered professional ambitions and personal hopes in order to meet expectations of others. We have learned to be highly organized coordinators and jugglers, even jesters. A sense of humor can wear thin, however.

All physicians need to press on with resolve. We should attend to language, to words. Thoughtless words can degrade. Instead, words should encourage and show respect. But good words are only a start. We also must act. Action should promote progress. Doors must be opened and runways cleared. Women physicians have come far—and have a long way to go. The way can be smoothed by men and women with spirit, with the will to move ahead.

LINDA HAWES CLEVER, MD

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Physicians and the Human Immunodeficiency Virus

THE MAGNIFYING GLASS of the acquired immunodeficiency syndrome (AIDS) epidemic has increasingly become a looking glass as well, reflecting physicians' attitudes and behaviors and society's reaction to them. The image we see, particularly regarding those physicians who are infected with the human immunodeficiency virus (HIV), is neither clear nor necessarily encouraging. Yet some clarity is urgently needed—some physicians *are* HIV infected, others will become infected, and as they become aware of their infection, it seems unfair not to provide some clear standards of behavior if they wish to continue and are otherwise capable of continuing to practice their profession. The unacceptable alternative is to let the appropriateness of each infected physician's response be judged by the public through the news media as the disease progresses to the point where confidentiality is no longer possible. It is hoped that a better understanding of the individual components of this social equation might enable the medical profession to instead play an active and leading role in proposing solutions that are fair to affected physicians and reassuring to patients.

Many physicians see themselves as selfless and devoted through their profession to the care of others. Limitations to this self-view became obvious, however, as soon as the infectious nature of AIDS was clear. Each of us feared for our safety, and some physicians—overtly in some cases, covertly in others—found ways to avoid caring for AIDS patients, even if the resulting quality of delivered medical care suffered. To justify these ignoble actions, some physicians have publicly exaggerated the risks posed by caring for HIV-infected patients. Some of the embellishment has been due to fear, some due to homophobia. There has also been the implication that physicians (usually internists) who do not join in these claims are unsympathetic to their surgical colleagues. Worse is the implication that physicians caring for HIV-infected patients are under the influence of the gay community. The argument goes that the gay community is more concerned about receiving confidential medical care than it is about the risk its members might pose to physicians. These

arguments begin to split physicians from patients and from each other.

Recognizing and correcting homophobia may be difficult for many, but insisting on actual data regarding transmission risk should be easier. Here, with respect to the risk of physicians acquiring HIV from patients, the data have been increasingly reassuring. Even orthopedic surgeons, argued by some to be at a theoretically high occupational risk, have been shown to be free of HIV unless they have had nonoccupational transmission-prone behaviors. The *documented* degree of risk, as opposed to the *speculated* risk, is insufficient as the basis for compromises in patient confidentiality or limitations in access to optimal medical or surgical care. Similarly, evidence of any benefit to physicians from routine nonvoluntary testing and reporting of patients for HIV is also lacking.

Now that data show the limited risk of transmitting HIV from patients to professionals, the number of calls for involuntary HIV testing and reporting of patients has decreased. Our current situation with HIV-infected physicians appears at first to be very different. The transmission of HIV to patients in the office of an infected dentist is recognized to have occurred. Instead of physicians being afraid, patients are now afraid. Instead of patients putting physicians at risk because of their socially disapproved behaviors, medical professionals are portrayed as irresponsible and selfish and willing to put their patients in jeopardy to protect their own privacy and careers. If opinion polls are to be believed, 90% of all adult Americans believe that something needs to be done to protect them from their physicians. In a rapid response, especially following the publication of these opinion polls, draconian (Helmsian) bills criminalizing the practice of medicine have passed the US Senate, and even the most moderate positions taken by the Centers for Disease Control, the American Medical Association, and the Senate "leadership" bill would probably eventuate in mandatory physician HIV testing, at least in some states, and an essentially forced termination of practice. How confident are we that when left to local specialty boards, "exposure-prone procedures" will not include essentially all surgery? Recall the Chicago physician with HIV for whom "invasive" procedures included routine oral examination with an instrument no sharper than a tongue depressor.

Is all of this necessary? Will we look back at these measures as appropriate and useful in instilling public confidence in the medical profession? Or will we see it as an overreaction that perpetuates the fractures of the medical communities and abdicates responsibility for the profession and for public health in favor of momentarily popular and political forces? Certainly our past experience with physicians' fears of patients might have taught that data can be reassuring, not just alarming, and that initial reactions in the absence of data might be based more on fear and discrimination.

Given that, what is the strength of the current data on the risk physicians might pose to patients? Five patients were infected in one dentist's office, but not one of the hundreds of other patients of HIV-infected surgeons who have been "recalled" for testing are reported to have acquired HIV. Many physicians, on receiving an HIV-positive report, immediately ask themselves whether they should alter their practice. Some have done so, whereas others—again after careful consideration and consultation with AIDS experts—decide to continue their careers, believing that the care they provide outweighs the remote risk of transmission. Some of these conscientious physicians nevertheless live in mortal fear that they will be publicly exposed, humiliated, and ruined.

Most American adults may be afraid, but perhaps they are also wrong. Knowing how little data are now available, we can at least assume that public opinion is not fully informed. We might also believe that it recognizes neither the potential harm in taking the wrong steps at this time nor that other approaches are possible. The media will forget about HIV-infected physicians, as they have forgotten about other health-related issues after an amazingly short period. With more time and data, public opinion will also change rapidly. Most physicians will continue to act in their patients' and their own best interests. Physicians will be voluntarily tested for HIV in confidential settings, and they will use this information to adjust their practices if they think they pose any risk to their patients.

Meanwhile, the medical profession must stop reacting to uninformed political pressure and insist that it can and must deal with this issue itself. As voluntary guidelines are established, physicians can vigorously and quickly collect additional information. They can develop a consensus about the degree of risk that can be tolerated, as is done for other common conditions that might impair a physician's performance and hence patients' safety. In a sense, the difficulties of charting a course on the current debate and the scrutiny physicians are under offer unique opportunities. If the medical profession succeeds in creating an informed public and political opinion and if rational policies result from this, at least some pride in its leadership could be restored. Also, if it is insisted that standards of safe physician behavior be developed beyond those that simply address HIV, the overall quality of medical care can benefit from these efforts.

PAUL A. VOLBERDING, MD
Professor of Medicine
University of California, San Francisco, School of Medicine
Director, AIDS Program
San Francisco General Hospital Medical Center
San Francisco, California

Liver Transplantation—Challenges for the Future

ORTHOTOPIC LIVER transplantation (OLT) is the accepted treatment of a variety of irreversible acute and chronic liver diseases for which no other form of therapy is available.[1-3] Liver transplantation was initiated nearly 30 years ago when the first human OLT was performed by Starzl in 1963; survival for more than a year was not achieved until 1967, however. The one-year survival rate following OLT was approximately 30% before 1980 but increased to 65% in the early 1980s at the University of Pittsburgh (Pennsylvania).[1] These improved results led a consensus development conference of the National Institutes of Health to conclude in June 1983 that liver transplantation was no longer experimental.[4] This conference was instrumental in broadening funding for the procedure by health insurance carriers and government agencies and in stimulating the development of more transplant centers, resulting in the increased availability and performance of liver transplantation.[5] In 1989, a total of 2,162 liver transplantations were done at 69 transplant centers in the United States; in 1990, there were 2,656 liver transplants performed, a 23% increase over the previous year. In 1989, about 60% of liver transplant procedures in the United States

were performed at 10 centers doing 50 or more per year, and 40% were carried out in the remaining 59 smaller, and often newer, programs. Liver transplant programs are now situated in most major metropolitan areas in the US, and OLT is considered in virtually every patient with irreversible acute and chronic liver disease. As demonstrated by Szpakowski and co-workers elsewhere in this issue of the journal, new liver transplant centers can achieve excellent results—that is, an 85% two-year survival.[6]

Currently more than 80% of private insurance carriers provide liver transplant coverage. Medicare limits coverage for the procedure to federally designated medical centers and restricts the underlying causes of liver diseases that qualify—postnecrotic cirrhosis associated with the presence of hepatitis B surface antigen and primary hepatic malignancy are excluded. Organ transplantation is an optional benefit under the Medicaid program; most states, however, provide coverage for OLT, although about 20% of states limit it to children only. Finally, a substantial number of Americans are uninsured, and insurance does not fully cover the total costs of OLT. Thus, significant gaps remain in coverage for the procedure; the challenge of the 1990s is to close this gap. The current 75% to 80% survival rate three to five years following the operation and the results of quality-of-life studies showing that more than 85% of patients are able to return to work[7] should be an impetus to broaden coverage for the procedure.

Another important challenge, as organ donation rates stabilize and waiting lists continue to grow, is to increase the number of donors. For too many potential liver transplant recipients, particularly children, the wait for a donor liver proves fatal. It is estimated that between 20,000 and 25,000 of the 2.2 million Americans who die each year meet age and medical criteria that would allow organ donation, but the number of organ donors in 1989 to 1990 was only about 6,000.[5] In recent years, several measures have been adopted to increase organ donation: incorporating donor cards onto drivers' licenses, distributing donor cards by hospitals and other groups, and enacting required request laws. More innovative approaches are needed to further promote donation and relieve the increasing shortage of organs.

New operative procedures have been developed in the past few years to alleviate the shortage of size-matched organ donors for children.[8,9] Reduced-size OLT is a procedure in which part of the liver graft is reduced by dissecting appropriate right or left lobe anatomic segments and then implanting in the orthotopic position after total recipient hepatectomy. It is also possible to obtain two grafts from a single donor, known as the "split-liver" procedure.[8] Another approach to the scarcity of infant and child donors is transplantation of a liver graft from a living related donor.[9] The donor undergoes a resection of the left lateral segment of the liver, which is then transplanted into the recipient. Experience with this approach is increasing in the United States at the University of Chicago Hospitals, and the ethical issues are being addressed.

Introduction of the University of Wisconsin (UW) solution is another new development that has revolutionized liver transplantation.[10] In an experience with liver homografts preserved for 4 to 24 hours with UW solution compared with grafts preserved for 3 to 9 hours with conventional Euro-Collins solution, the UW-preserved grafts had a lower rate of primary nonfunction with a reduced need for retransplantation.[10] In addition, the UW solution has improved donor operation logistics, reduced the costs of transplantation, and allowed a semielective approach to liver transplantation. In the 1990s, we may witness the discovery of even better organ-preserving solutions.

The overall goals of OLT are to prolong life and improve the quality of life. The selection of appropriate patients to achieve these goals is difficult and inexact, with no uniformly agreed-on national criteria. Even more troublesome is determining the appropriate timing of liver transplantation during the course of advanced chronic liver disease. General indications for liver transplantation in adults are as follows[1-3]: irreversible advanced chronic liver disease, fulminant hepatic failure, unresectable hepatic cancer confined to the liver, and metabolic liver disease. In addition, there should be no contraindications to the procedure and the patient should be able to provide for its costs. The absolute and relative contraindications to OLT have evolved over the past ten years of cumulative experience. The usual absolute contraindications include the following[1-3]: the acquired immunodeficiency syndrome or human immunodeficiency virus positivity, malignancy outside the liver, uncontrollable infection outside the hepatobiliary system, active alcoholism or intravenous drug abuse, and advanced cardiopulmonary disease. Relative contraindications or conditions that complicate and increase the risk of transplantation include advanced age, stage III to IV hepatic coma, advanced chronic renal failure, hypoxemia from intrapulmonary shunts, portal vein thrombosis, previous portosystemic shunt operation, previous biliary tract operation, severe malnutrition, and massive ascites.

Guidelines are needed for referring patients with fulminant or chronic end-stage liver disease for OLT.[11] The optimal timing of the procedure requires a knowledge of prognostic indices and the natural history of each specific liver disease suitable for transplantation. The best application of prognostic survival models to the timing and outcome of OLT in chronic liver disease has been applied to primary biliary cirrhosis, a disease with the most predictable natural history.[12,13] The application of the Mayo Clinic model, which includes five independent prognostic variables (serum levels of bilirubin and albumin, prothrombin time, age, and the presence of peripheral edema), has demonstrated that the procedure improves survival compared with supportive therapy in patients with primary biliary cirrhosis.[12,13] Primary sclerosing cholangitis has a less predictable natural history because of a fluctuating course and the possibility of cholangiocarcinoma developing, but similar independent predictors of prognosis can be identified.[14] Investigators at King's College Hospital in London have proposed specific demographic and laboratory criteria for liver transplantation in patients with fulminant hepatic failure based on a large and longitudinal experience.[15] Separate criteria have been established for patients with fulminant hepatic failure due to acetaminophen overdose and those with failure caused by viral or drug-induced hepatitis. Clinical judgment and assessment of the patient's quality of life, important factors not found in any of the current models, will likely remain critical in deciding the timing of OLT, but they require standardization.

Immunosuppressive drug regimens vary from center to center but generally include corticosteroids, cyclosporine, and azathioprine. Corticosteroids are used initially in high doses, which are progressively reduced to maintenance levels of 10 to 20 mg daily during the initial several months after the operation and then to 5 to 10 mg daily long term. Cyclo-

sporine is administered at a dose to maintain therapeutic trough levels, and its use is often begun postoperatively only after adequate urinary output is established. Several centers use so-called triple therapy with azathioprine, which allows the use of lower doses of all three drugs, thus avoiding toxicity of individual agents. A recent immunosuppressive variation is the use of prophylactic OKT3 for 7 to 12 days following the operation, with the later introduction of cyclosporine. In general, however, OKT3 is reserved for episodes of rejection. In this decade, three new candidate immunosuppressive drugs have been developed: FK 506,[16] rapamycin, and 15-deoxyspergualin. FK 506 appears to be the most promising, both as an agent to reverse rejection unresponsive to conventional drugs and as primary immunosuppressive therapy to achieve better patient survival and fewer episodes of rejection. Multicenter studies are under way in Europe and the United States to determine the efficacy of FK 506 compared with cyclosporine and to better define toxicity. The treatment of rejection episodes following OLT typically includes giving a bolus of corticosteroids, sometimes followed by an oral recycle of high doses with rapid tapering back to a maintenance level, the use of OKT3, and retransplantation. These treatments are usually applied in a stepwise fashion. With refinements in the indications, timing, and technical aspects of the procedure, the scarcity of organs and the precise diagnosis and optimal management of rejection loom as the major challenges of transplantation.

There are several controversial areas in liver transplantation today. Alcoholic cirrhosis is the leading cause of hepatic morbidity and mortality in the US. The major deterrents to liver transplantation in patients with alcoholism are concerns regarding abstinence after transplantation and the possible presence of medical problems associated with chronic alcoholism, such as pancreatitis, cardiomyopathy, neuromuscular syndromes, or severe malnutrition. In a recent report by Starzl and colleagues, of 41 patients with alcoholic cirrhosis treated with liver transplantation, 73% were alive at one year and 68% between one and three years.[17] These results were no different from those obtained in 625 adult patients who received liver transplants for other reasons. Moreover, of 35 patients who survived longer than six months, only 2 returned to active alcoholism. These preliminary results, which require verification in other centers and longer periods of follow-up, have led to the consensus that patients with end-stage alcoholic liver disease should not be excluded from consideration for liver transplantation. The current policy of many transplant centers is to require some period of alcohol abstinence, typically six months, to mandate involvement in a structured alcohol rehabilitation program and to verify that the patient has a stable and supportive psychosocial structure.

Hepatitis B typically recurs after liver transplantation, and the long-term survival of patients (45% to 50%) is substantially less than for patients receiving transplants for other causes of end-stage liver disease (75% to 80%).[18] Efforts to treat hepatitis B infection perioperatively or postoperatively with hepatitis B immune globulin or interferon alfa have generally failed. Not all centers continue to do OLT in patients with hepatitis B, and newer experimental modalities to prevent or treat recurrent hepatitis B are desperately needed. Although data are preliminary, the hepatitis C status of the donor and recipient appear to have little bearing on the subsequent course following the operation. One large retrospective study found that the loss of antibody to the hepatitis C virus (anti-HCV) was frequent and acquisition of anti-HCV rare following the procedure. The development of hepatitis after transplantation was unrelated to the anti-HCV status.[19] There are no data that suggest a lower survival rate following OLT for postnecrotic cirrhosis due to hepatitis C, but longer follow-up with surveillance using more sensitive serologic assays is needed.

Although transplantation for hepatocellular malignancy has a long-term survival that is inferior to all other indications for liver transplantation, selected patients may obtain meaningful palliation and even long-term survival. Survival is distinctly better in those patients receiving transplants for hepatocellular carcinoma compared with that for cholangiocarcinoma.[20] Certain tumor types have a favorable prognosis—hemangioendothelioma, fibrolamellar hepatocellular carcinoma, and incidental hepatocellular carcinoma—and remain excellent indications for liver transplantation. In the 1990s, it is desirable that all patients with hepatocellular carcinoma be placed on experimental adjuvant therapy protocols to accumulate data regarding the possible benefits of such therapy. Orthotopic liver transplantation for cholangiocarcinoma or for primary diseases metastatic to the liver should be considered investigational.

As demonstrated in the report of Szpakowski and associates, transplantation can be carried out with excellent results in a new liver transplant center at a private medical center.[6] The two critical factors that determine the success of a new program are the training and experience of the transplant surgeons and a full institutional commitment. These good results may have been influenced in part by selection factors—a third of the patients were children, and only one patient underwent OLT for primary hepatic malignancy. On the other hand, seven patients had hepatitis B; six were reinfected, and three died. It should be pointed out to skeptics that all 11 patients with alcoholic cirrhosis survived, and only 1 returned to drinking. Finally, the immunosuppressive regimen using prophylactic antilymphocyte globulin, cyclosporine, and low-dose corticosteroids was associated with a low rate of fungal and viral infections and likely contributed to the excellent outcome of these first 100 liver transplant operations.

EMMET B. KEEFFE, MD
Professor of Medicine
Division of Gastroenterology
Oregon Health Sciences University
Portland, Oregon

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Molecular Genetics in the Cancer Clinic

THE INCORPORATION OF modern molecular approaches into research on clinical problems is now extensive. Indeed, one can hardly read a medical journal these days without at least a general understanding of the various techniques in molecular biology. This is arguably as true for investigations of the neoplastic diseases as it is anywhere, perhaps reflecting a relatively early appreciation that malignant neoplasms are, in essence, genetic disorders. Many results of "basic" research on the molecular mechanisms of oncogenesis are rapidly approaching the point of clinical application in the diagnosis and management of human cancer. This work is thus of more than passing concern to physicians who care for patients in their practice with cancer. The literature in this discipline is vast and often minutely focused, however, and so is not always readily accessible to interested clinicians. In this issue of the journal, Koeffler and colleagues have distilled from this mass of information a usefully concise and current summary of the genetic lesions that have been identified in human tumors.[1] They also touch on many of the ideas that these findings have prompted regarding molecular mechanisms in the pathogenesis of cancer. Several of the models that the authors discuss are particularly useful in their generality. I wish to illustrate this point by reviewing some important related findings published too recently for inclusion in their article.

Chromosomal Translocations in Oncogenesis

The finding of a given chromosomal translocation (at the cytogenetic level) in multiple independent specimens of the same tumor type is strong circumstantial evidence for participation of the associated genes in the origin or progression phase of tumorigenesis. Molecular analysis of such recurrent translocations is a venerable, and still fruitful, approach to the isolation of novel genes involved in oncogenesis. This has been particularly true for the lymphoid neoplasms, where one partner in the translocation is frequently an immunoglobulin or T-cell receptor *(TCR)* gene. These can serve as a toehold from which it is possible to "walk" across a cloned translocation break point to the candidate proto-oncogene.

Translocations with gene deregulation. As noted by Koeffler and associates, juxtaposition of the c-*myc* locus with the immunoglobulin heavy chain *(IGH)* gene (as in Burkitt's lymphoma) may be regarded as the prototype of situations in which proto-oncogenes suffer deregulation as a consequence of translocation.[1] In instances such as these, the cognate oncoprotein gene products are inappropriately expressed, but they are not physically altered. Several recently described cases of this pathogenic mechanism have made for interesting additions to the list of cellular functions that are apparently oncogenic when corrupted in this context. For example, *BCL2*—a gene "activated" by translocation to the *IGH* locus in most follicular malignant lymphomas—encodes a mitochondrial protein somehow involved in governing B-lymphocyte lifespan[2,3]; overexpression of *BCL2* protein in association with the translocation seems to block programmed cell death in this lineage. This leads in turn to a pathologically expanded B-cell population by decreased attrition rather than increased proliferation.[2,3]

The *BCL1* gene, yet another gene sometimes juxtaposed with the *IGH* locus in lymphoid malignant diseases, codes for a member of the cyclin protein family.[4] Several of the cyclins are known to be intimately connected with the regulation of cell-cycle progression in eukaryotes. The *BCL1* locus is also amplified (without known translocation) in a number of nonlymphoid tumor types.[4] The exact role of *BCL1* deregulation in tumorigenesis is by no means clear at present. It is an intuitively appealing notion, however, that cyclin function could sustain derangement in neoplastic cells, leading to the loss of a normal control of proliferation.

A recurrent translocation of T-cell acute leukemia situates a *TCR* locus adjacent to a so-called homeobox *(HOX)* protein gene.[5] The many *HOX* family proteins appear to figure prominently in regulating cell type-specific differentiation during development. Here, too, nothing is certain regarding detailed pathogenic mechanisms of tumorigenesis supported by the translocation. It is interesting to suggest, though, that this is a case where the abrogation of normal differentiation (perhaps an interfering effect of the inappropriately expressed *HOX* protein), rather than a loss of proliferation control per se, is the root cause of neoplasia.[3,6]

Translocation with protein alteration. Chromosomal translocation can also lead to the synthesis of a functionally abnormal and pathogenic fusion protein; the *BCR/ABL* products in acute lymphocytic and chronic myelogenous leukemias[7] are discussed by Koeffler and co-workers as models for this mechanism of neoplastic change.[1] As another example, the breakpoint of the t(15;17) translocation of acute promyelocytic leukemia occurs in the retinoic acid-receptor-α locus *(RAR)*.[3,8] This is intriguing because retinoic acid and its analogues are known to be potent inducers of differentiation in primitive myeloid cells.[3,8] The translocation event leads to the formation of a protein in which aminoterminal sequences of *RAR* are replaced with those of a previously undescribed gene designated *MYL*.[8] While the *MYL/RAR* fusion protein, like the parent *RAR* protein, can mediate the regulation of gene expression by retinoic acid, its function in this respect is clearly abnormal.[8] It is possible that the *MYL/RAR* fusion protein acts in an inhibitory way in promyelocytic leukemia cells by outcompeting normal *RAR* molecules. The latter would otherwise affect progress along the myeloid differentiation pathway.[3,8] It has recently been found that administering all-*trans*-retinoic acid induces complete remission in a large proportion of patients with acute pro-

myelocytic leukemia who have the *MYL/RAR* translocation.[9] It remains to be determined whether this reflects augmented in vivo function of *MYL/RAR* protein, of normal *RAR* protein, or neither of these.

Tumor Suppressor Genes

Retinoblastoma. Koeffler and associates discuss retinoblastoma *(RB)* as a paradigm for the isolation of tumor suppressor genes connected with an inherited susceptibility to cancer. The genetic basis of familial retinoblastoma was understood first at the clinicoepidemiologic level, next at the cytogenetic level, and finally, with the cloning of the *RB* gene, at the molecular level.[6] Subsequent studies of this disorder have led to a key realization: a tumor suppressor gene involved in a heritable cancer-prone diathesis can also be important in sporadic (nonfamilial) tumorigenesis. This result is of considerable practical importance because sporadic cancers are much more common than familial ones. Interestingly, these sporadic tumors are often of histologic types different from those found in the inherited cases.

Neurofibromatosis and familial adenomatous polyposis. Two additions have been made to the list of cloned human tumor suppressor genes provided in the article[1]: *NF1*, associated with type I neurofibromatosis,[10,11] and *APC*, associated with adenomatous polyposis coli (also known as familial adenomatous polyposis).[12,13] Each of these disorders confers heritable susceptibility to specific tumors. In contrast to *RB*, where the position of the gene could be inferred initially from karyotypic studies, the *NF1* gene chromosome assignment (17q11.2) was educed by genetic linkage analysis of affected families (subsequent identification of patients with translocations in this area further refined the localization) (reviewed by Marshall[6]). The finding of mutations in exonic (messenger RNA-encoding) gene sequences in this region in patients with neurofibromatosis, but not in normal subjects, positively identified the *NF1* gene.[6] Sequence analysis revealed that the *NF1* gene product has significant structural homology to *gap*—the *ras*-associated guanosine triphosphatase-activating protein discussed in the article.[1] Models proposed for the function of *NF1* and for its dysfunction in neurofibromatosis-associated tumors[6] are analogous for those noted for *gap*.[1]

Previous cytogenetic and linkage analyses had localized the gene for susceptibility to familial adenomatous polyposis *(APC)* to chromosome 5 at band q21.[6] This chromosomal locus was noted by Koeffler and colleagues in two connections[1]: heterozygosity at 5q21 in sporadic colorectal carcinomas is frequently lost, and this is the location of the putative colorectal tumor suppressor gene *MCC*. It had been cautiously suggested that *MCC* might itself be the gene *(APC)* associated with familial adenomatous polyposis. It is now evident, however, that *APC* is distinct from (but closely adjacent to) *MCC*.[12,13] It appears that, while both of these genes can be altered in sporadic colorectal carcinomas, only *APC* is abnormal in the germ line of families with familial adenomatous polyposis. Nothing is yet known about the functions of these genes.

p53 Tumor suppressor gene and familial cancer. The p53 locus has provided an interesting twist to studies on the genetics of heritable neoplasia: here it was the understanding of a gene that prompted the search for a disease, rather than the reverse. A number of results—reviewed by Koeffler and colleagues[1]—had strongly indicated that the normal p53 gene product functions as a tumor suppressor. By analogy with retinoblastoma, it was therefore reasonable to postulate that inherited mutations in the p53 gene are the basis of other familial cancer-prone disorders. This has been found to be the case. In two studies, families fitting the clinical criteria for the Li-Fraumeni syndrome—a rare but well-described condition predisposing to certain tumors including breast carcinoma, sarcoma, and glioma—were shown to carry germ-line mutations in p53.[14,15] In a third study, germ-line mutation of p53 was found in a boy with an ependymoma who was from a cancer-prone family. This tumor and those of several of his relatives had not been strongly associated previously with the Li-Fraumeni syndrome.[16] To reconcile these results, it is tempting to speculate that the various mutant p53 alleles present in different cancer-prone families might predispose to distinct tumor types. It is also interesting to consider the possibility that some germ-line mutations of p53 (and other tumor suppressor genes as well) may have less severe phenotypic effects than others. Such a situation might account for families wherein cancer seems to be frequent or to strike the relatively young but not so dramatically as in the prototypic cancer-prone diseases noted earlier. Recent laboratory evidence supports this concept of mutation-specific differences in the biologic properties of different p53 alleles.[17]

Future Prospects

For information about tumor genetics to be most useful in clinical practice, the respective molecular analyses would ideally be done with the speed and reliability of present hospital laboratory tests (or nearly so). Recent technologic advances and the development of molecular diagnostics as a clinical specialty make this goal conceivable. The polymerase chain reaction method—discussed by Koeffler and colleagues in connection with tumor *ras* gene mutations—is especially noteworthy in this regard as it has decreased the time scale of some manipulations from days or weeks to hours. As a current example, by using the polymerase chain reaction, the presence of the Philadelphia translocation in a specimen can now be assessed overnight; this is sufficiently rapid to permit inclusion of the result in the selection of initial therapy for a newly diagnosed case of acute lymphoblastic leukemia.[18] Other breakthroughs are likely to follow in the foreseeable future. As readers of the article will appreciate, this is indeed a time when both oncologists and basic molecular biologists can share in the excitement and optimism as the genetic mechanisms of cancer become better understood.

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ERIC H. RADANY, MD, PhD
Department of Radiation Oncology and the G.W. Hooper Research Foundation University of California, San Francisco San Francisco, California

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Correspondence

The Editors will be pleased to receive and consider for publication correspondence containing information of interest to physicians or commenting on issues of the day. Letters ordinarily should not exceed 600 words and must be typewritten, double-spaced, and submitted in duplicate (the original typescript and one copy). Authors will be given the opportunity to review the editing of their correspondence before publication.

Human Immunodeficiency Virus Infection in Children Who Received Transfusions in Mexico

To THE EDITOR: We report the cases of four children who received blood transfusions in Mexico and in whom human immunodeficiency virus (HIV) disease subsequently developed.

Summary of Cases

Patient 1 presented at 8 months of age with a history of chronic diarrhea, oral candidiasis resistant to therapy, failure to thrive, and hepatitis. She received approximately 20 ml of blood at 2 months of age for anemia and respiratory distress.

Patient 2 presented at 4 years of age with recurrent disseminated varicella-zoster. He also had a history of chronic diarrhea and a urinary tract infection. He received an unknown amount of blood in a transfusion for anemia at 6 months of age.

Patient 3 was seen initially at 4 years of age with stage IV Burkitt's lymphoma. He was in remission after chemotherapy and surgical therapy when a year later he had metastatic B-cell leukemic relapse. At the time of the progressive disease, the diagnosis of the acquired immunodeficiency syndrome (AIDS) was made. He had received a transfusion at 21 months of age for diarrhea and dehydration.

Patient 4 presented at 4½ years of age with chronic otitis media and mastoiditis, oral candidiasis, chronic diarrhea, herpetic gingivostomatitis, pneumonia, and a loss of a third of his previous weight over a three-month period. He had received a blood transfusion at 6 months of age for diarrhea and dehydration.

All four of these patients were transfused at different institutions in Guadalajara, Mexico (Osmar Matsui-Santana, MD, Instituto Regional de Investigacion en Salud Publica, Universidad de Guadalajara, written communication, December 1989) in 1986 and 1987 (patient 4). All the patients were documented infected by enzyme-linked immunosorbent assay (ELISA) and Western blot (patients 2, 3, and 4) or by direct HIV culture (patient 1). Each had significant immune function abnormalities at presentation, including reduced percentages of circulating $CD4^+$ "helper" T cells (range <1% to 29%) and hyperimmunoglobulinemia (patients 2, 3, and 4) or hypogammaglobulinemia (patient 1). The mothers of the patients were either negative for HIV antibody by ELISA (patients 2, 3, and 4) or had no other identifiable risk factors for AIDS (patient 1).

The routine screening of blood for the HIV antibody in the United States began in March 1985.[1] The chances of receiving an HIV-infected blood product here are small[2] and seem to be decreasing.[3] The odds are lower than for most other transfusion-associated complications.[4] This may not be the case in other countries, however. In many of the 152 countries that have reported at least one case of AIDS,[5] the screening of blood products began after March 1985 or has not yet begun at all.

As our four cases show, HIV testing should be considered in any person who was transfused in a country where the screening of all blood for HIV was not routine at the time of transfusion. The screening of blood for HIV was not instituted in Mexico until mid-1986, and private paid blood donor centers were not closed until 1987.[6] Up to 30% of paid blood donors at one center were positive for HIV antibody in Guadalajara during the same year these four children were transfused.[5]

The diagnosis of HIV infection may be delayed or overlooked entirely in children who have no other risk factors for AIDS than an apparently "safe" blood transfusion. As the development of AIDS or symptomatic HIV infection can occur as long as seven years or more following an infected transfusion,[7] one can expect additional transfusion-associated cases to present well into the mid 1990s from Mexico alone, perhaps later from other countries. Indeed, patient 4 was first seen in February of 1991. Furthermore, children infected from mothers who themselves were infected through blood transfusions after 1985 may present even further in the future.

When evaluating a patient for AIDS risk factors, physicians should ask for both the time and place of any transfusion. Patients planning foreign excursions should be advised about the safety of the blood supply in those particular locales.

RONALD M. FERDMAN, MD
JOSEPH A. CHURCH, MD
Division of Allergy-Clinical Immunology
Department of Pediatrics
Childrens Hospital of Los Angeles
University of Southern California School of Medicine

LAURENE MASCOLA, MD
Los Angeles County Department of Health Services

JUDITH K. SATO, MD
Division of Hematology-Oncology
Department of Pediatrics
Childrens Hospital of Los Angeles
University of Southern California School of Medicine

PO Box 54700, Mail Stop #75
Los Angeles, CA 90054-0700

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Toxic Exposure to Betamix

To the Editor: I would like to report a toxic occupational exposure to an agricultural chemical that might be of interest to other journal readers. The case involved the development of allergic rhinitis, allergic dermatitis, and toxic hepatitis after use of the sugar beet herbicide Betamix—a mixture of the carbamates phenmedipham and desmedipham.

The patient, a 39-year-old man, initially sought medical care for fever, severe headache, diffuse arthralgias, persistent emesis, persistent sneezing, and a pruritic rash covering most of his body. His symptoms started within 48 hours of applying the herbicide to a sugar beet field. The patient said he did not use a mask and was not wearing protective clothing. A much briefer exposure to the chemical a month earlier resulted only in mild headache and arthralgias.

Clinical findings at the time of initial presentation included fever to 38.8°C (101.9°F), signs of allergic conjunctivitis and rhinitis, right upper quadrant pain, and a total-body macular-papular rash with scattered urticaria. The rash involved both exposed and nonexposed body areas with papules ranging from 0.5 to 2 cm in diameter and surrounding erythema varying from 2 to 4 cm.

Neurologic examination results were completely normal, and, despite the patient's symptoms, there was no joint swelling or redness and only minimal tenderness.

Laboratory findings included a normal complete blood count; urinalysis with 8 to 10 leukocytes, 1 to 2 erythrocytes, and no bacteria; an erythrocyte sedimentation rate of 28 mm per hour; and normal chemistry values—except for liver function tests. These revealed an alkaline phosphatase level of 166 U per liter, aspartate aminotransferase 55 U per liter, alanine aminotransferase 113 U per liter, and γ-glutamyl transferase 263 U per liter. Culture of the urine showed no growth. A complete viral hepatitis panel was negative.

The patient repeatedly denied anything more than occasional, moderate use of ethanol. His wife confirmed that he drank two to four beers a week. Both said independently that the patient had not taken any alcohol since his first herbicide exposure the previous month. He had no other known chemical, environmental, or infectious exposure of any kind.

Because of financial limitations, the patient was not admitted to hospital but was instead observed closely with several clinic visits. Intravenous fluids, along with parenteral and oral analgesics, antiemetics, and antipruritics, were used as needed.

Over the first week after the initial presentation, headache symptoms were replaced by right upper quadrant pain as the fever subsided. The patient's nausea and pruritic rash slowly resolved over several weeks. By one month after the initial presentation, the patient's abdominal pain had fully resolved and his liver function test results had returned to normal. He continued having pronounced symptoms of allergic rhinitis, however, which he had never had before.

No other agricultural workers with similar symptoms were seen at our clinic. The case was reported to the Idaho Department of Agriculture, where the patient was interviewed at length but provided no additional information.

A review of the recent literature yielded only one report of a serious reaction to the active ingredients of Betamix.[1] These investigators reported in the German dermatologic literature a case of photoallergic dermatitis and hepatitis in a German woman who had used phenmedipham.

I would like to add this case to the growing number of known toxic agricultural chemical exposures. With the continuing development of new mixtures and products, other new reactions are likely to occur.

MARC TUNZI, MD
Family Health Services
542 Main Ave South
Twin Falls, ID 83301

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Smoking Cessation Attitudes, Practices, and Policies Among California Primary Care Physicians

To the Editor: Recent studies have endorsed physician intervention as an important addition to smoking cessation efforts because of physicians' ability to reach large populations.[1-4] If smokers require medical care at least as frequently as nonsmokers and if physicians advise them during routine care to quit smoking, approximately 38 million of the 54 million smokers could be reached in a single year. A long-term success rate of even 5% to 10% would mean that 1.9 to 3.8 million persons would quit smoking.[5]

Under the auspices of California's Proposition 99, the Tobacco Tax Initiative, a 32-item questionnaire was developed to ascertain attitudes, practices, and policies related to tobacco control of primary care physicians in California. Primary care physicians were defined as active physicians in general practice, family practice, internal medicine, obstetrics and gynecology, or pediatrics. Using a California Medical Association mailing list, 5% of primary care physicians were randomly surveyed in July 1990, resulting in a total sample of 1,680 physicians. Follow-up surveys were sent to all nonrespondents, and 10% of the nonrespondents were surveyed over the telephone.

Of the 1,680 physicians contacted, 581 (35%) responded. Of these, 423 (74%) physicians were in practice, and our results are based on these physicians. The mean age of the respondents was 47 years. Most were male (82%) and non-Hispanic white (80%).

With regard to office smoking policies, 401 (94%) physicians reported that patients were not allowed to smoke anywhere in the office. Few had a designated smoking area in the office, and 355 (83%) did not allow staff members to smoke anywhere in the office. Of responding physicians, 330 (78%) had "no smoking" signs in their waiting rooms, and 234 (55%) had brochures or pamphlets in their waiting rooms for stopping smoking. Only 155 (36%) physicians had a list of community resources for smoking cessation available to patients.

Of these physicians, 253 (60%) reported that there was no routine system in their office to identify tobacco users by glancing at patient charts, but 379 (89%) said they routinely asked patients about their tobacco use. Those physicians who reported advising patients to quit using tobacco spent an average of 6 minutes doing so. The most common practices used by physicians to help patients quit smoking were informing patients of the benefits of quitting (93% advised most or all patients); recording results in medical records (81% did so for most or all patients); and advising patients to quit (94% told most or all patients).

Slightly more than half of the physicians thought they

were successful in helping patients to quit smoking. Physicians also agreed that it was their responsibility to convince tobacco-using patients to quit or help patients who wish to quit to do so and that they should be more active in speaking to lay groups about tobacco use.

While our response rate was low, these data do provide interesting information regarding tobacco control activities and policies of primary care physicians in California.

RUSSELL L. YOUNG, PhD
College of Education
San Diego State University
San Diego, CA 92182

CATHERINE CROOKS, PhD
JOHN P. ELDER, PhD, MPH
ERIN KENNEY, PhD, MPH
Tobacco Control Program Evaluation
Center for Behavioral and Community Health Studies
6363 Alvarado Ct, Suite 100
San Diego State University
San Diego, CA 92120

DILEEP G. BAL, MD
MICHAEL JOHNSON, PhD
California Department of Health Services
Tobacco Control Section
714 P St
Sacramento, CA 95814

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An Inexpensive, Convenient Adjunct for the Treatment of Diabetes

To the Editor: Two reports in this journal have strongly suggested that chromium picolinate supplements are beneficial in the treatment of hypercholesterolemia.[1,2] Clinical studies also suggest that chromium picolinate is highly beneficial in the treatment of non–insulin-dependent diabetes mellitus (NIDDM). In one study, 11 subjects with NIDDM were given either chromium picolinate (3.8 μmol [200 μg] of chromium) or a placebo daily for 42 days in a double-blind crossover study.[3] A 14-day period off capsules was used between treatments. The mean values for fasting blood glucose, glycosylated hemoglobin, total cholesterol, and low-density-lipoprotein (LDL) cholesterol decreased significantly while the subjects were ingesting chromium picolinate. The levels of these tests analyzed in three of the subjects either increased slightly or did not change. With the exception of high-density-lipoprotein (HDL) cholesterol and triglycerides, however, the blood values were decreased in the remaining eight during supplementation with chromium picolinate. Fasting blood glucose values in the eight responders decreased by 24% from a mean of 185 ± 16 mg per dl to a mean of 140 ± 18 mg per dl. Glycosylated hemoglobin levels in those eight decreased by 19%. Total cholesterol values decreased 13% from 230 ± 15 mg per dl to 200 ± 11 mg per dl, and LDL cholesterol values decreased 11% from 158 ± 8 mg per dl to 141 ± 7 mg per dl in those eight subjects.

In a second preliminary study, five American Indians with NIDDM from the Red Lake Minnesota Band of Chippewa Indians (1 man, 4 women) who had learned of chromium picolinate from health-care professionals or education classes volunteered to have blood analyses while using chromium picolinate supplements. After initial blood specimens were drawn, each of the volunteers ingested daily one capsule of chromium picolinate that contained 3.8 μmol of chromium. No other changes in dietary habits or exercise were initiated. After only two weeks, blood glucose levels had decreased markedly in each of the five volunteers. After eight weeks of supplementation, blood glucose values had decreased by 32.6% from a mean of 14.3 mmol per liter (258 mg per dl) to a mean of 9.3 mmol per liter (168 mg per dl). One of the female volunteers, who was being treated with 75 units of insulin per day, had an initial blood glucose level of 19.8 mmol per liter (357 mg per dl), but after eight weeks of chromium picolinate supplementation, her blood glucose value had decreased by 61% to only 7.6 mmol per liter (137 mg per dl). When these exceptional results were excluded, the blood glucose value of each of the other four was decreased by 25% from a mean of 12.9 (233) to 9.7 mmol per liter (175 mg per dl). Surprisingly, the total serum cholesterol levels in these volunteers were not in the "at risk" range but decreased by 8.2% from an initial mean of 4.7 mmol per liter (183 mg per dl) to 4.3 mmol per liter (168 mg per dl).

Although these two preliminary studies were conducted with a small number of volunteers, the high percentage of subjects responding (73% in one study, 100% in the other) suggests that chromium picolinate supplementation may be effective in regulating blood glucose levels and lipids in persons with diabetes. The results were particularly dramatic in the American Indians, a population that has a high incidence of NIDDM. The results described here show that large-scale trials are warranted for testing the efficacy and safety of chromium picolinate as a convenient, inexpensive adjunct to the treatment of diabetes.

GARY W. EVANS, PhD
Department of Chemistry
Bemidji State University
Bemidji, MN 56601

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The Digital Rectal Examination of Women

To the Editor: The article "Is deleting the digital rectal examination a good idea?" in the July issue discusses principally the discovery of abnormalities of the prostate. I address the subject as a gynecologist who has never examined a male patient.

During 50 years of practice as an obstetrician-gynecologist, it was my policy to make a digital rectal examination on every new patient, at every annual examination, and otherwise when indicated. I kept a record of positive findings but not of the number of examinations, but there were many thousands. In those 50 years I discovered three rectal polyps and I missed, in one sense, one rectal carcinoma. This patient complained of rectal bleeding; my rectal examination results were negative so I referred her to a proctologist who called me two hours later to say that he could feel a rectal mass. This

was a rectal carcinoma, which he removed. The patient lived for another ten years. Although I could not feel the tumor, a correct diagnosis was made the same day. In addition to these four cases, there were scores of rectoceles, enteroceles, and prolapses, most of which did not require rectal examination for diagnosis. One might take the view that in gynecology, rectal examinations are not "cost effective" except that if the gynecologist is already wearing a glove, the only cost is a few drops of lubricant.

Rectal examination of women is important for another reason. During my years in practice—when women were less outspoken than they are today—an admission of anal intercourse was the most difficult history for me to elicit. But if rectal examination revealed a decidedly relaxed sphincter without a history of a third-degree laceration, I could be pretty certain of anal intercourse, and then an oblique question, such as "Does your husband often approach you from the rear?" or "Do you object to rectal intercourse?" might confirm my opinion. Discussion of the acquired immunodeficiency syndrome (AIDS) often refers to "heterosexual transmission," which the reader may take to mean vaginal intercourse. The fact is that heterosexual anal intercourse is not rare and has the same potential for transmission of AIDS in heterosexuals as it does in homosexuals.

PENDLETON TOMPKINS, MD
49 Crystal Springs Rd
San Mateo, CA 94402-1518

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WARNING—Inhaling Tabasco Products Can Be Hazardous to Your Health

To the Editor: Laryngospasm is an occlusion of the glottis due to contraction of the intrinsic laryngeal muscles, thought to result from stimulation of the superior laryngeal nerve.[1] It is a well-known complication of anesthesia due to irritation of the vocal cords or nasal passages by anesthetic gases and can be produced by mechanical stimulation of the epiglottis during attempts at intubation or suctioning.[2] While laryngospasm is a protective reflex that prevents foreign matter from reaching the tracheobronchial tree, it can lead to respiratory arrest.

We report a case of acute laryngospasm associated with aspiration of a beverage spiked with Tabasco sauce.

A 33-year-old internal medicine fellow was reading while drinking V-8 juice liberally dosed with Tabasco brand hot pepper sauce when his elbow was jostled by his pet dog. As his elbow rose up—and the page with it—so followed his gaze, causing him to extend his neck. He began to exclaim to chasten the dog, but on inspiring, aspirated several milliliters of his drink. Attempting to cough, he found himself unable to breathe. Flexing the muscles of his neck did not alleviate the situation. He considered calling 911 but realized he could not speak. He continued to attempt respiration for 45 seconds and began to lose consciousness but finally succeeded in at first stridorous and then in increasingly normal respiration. He recovered without incident and did not seek medical attention.

Laryngospasm may have been caused by mechanical irritation of his larynx when he rapidly inhaled the drink, similar to the effect of intubation or drowning. Alternatively, either the capsaicin in the chili-containing Tabasco sauce or the acidic vegetable juice may have caused chemical irritation, as may also occur with the aspiration of gastric contents in patients with gastroesophageal reflux.[3]

To our knowledge, this is the first reported case of laryngospasm associated with consuming a Tabasco-containing product. Those who indulge in Tabasco-seasoned beverages should exercise caution when they sip. Tabasco, like tobacco, may be harmful when inhaled.

HAYA R. RUBIN, MD, PhD
ALBERT W. WU, MD, MPH
SEAN TUNIS, MD, MSc
Johns Hopkins University
624 N Broadway
Baltimore, MD 21205

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Lessons From the Practice

My Jogging Partner

DANA FREDERICK HOCH, MD, *San Jose, California*

I am a regular jogger. For the past few years, I've run with a couple of friends, an accountant and a lawyer. At 6 AM we meet at our athletic club and run 1½ miles to a local high school and back, plus 2 or 3 miles around the football field track. This morning ritual is as much a social as an athletic activity. We use the time to discuss work, politics, movies, and books.

One morning after a run, I noticed a new face in the locker room. I introduced myself to Joe. A slight, friendly appearing person, he was losing his hair and appeared older than 39. Joe had that sort of easygoing and genial manner that right away made me want to chat. I told him about our morning runs. Joe had been an athlete in high school and was eager to get back into jogging. He joined us in our morning run.

Joe had a natural and easy stride. After about a month he was pushing the rest of us a bit faster than we were used to. He quickly joined in and relished our morning dialogues. Lawyer, accountant, and doctor became his friends. He called us his "three amigos."

One morning I noticed Joe was oddly quiet and breathing particularly hard. He said he was tired and walked a lap. We continued on, sweating in the early morning coolness. Joe rejoined us, and we started back. I felt especially strong that day, and we were all pushing the pace. Joe's breathing took on a bit of a wheeze, and he dropped off the run a quarter of a mile from the club.

"I'll walk it in," he gasped. "See you inside."

We finished up, covered with sweat and that wonderful combination of exhaustion and "It-feels-so-good-when-it's-over" feeling.

"Let's go back and get Joe," the lawyer said.

We jogged back, fully expecting to see Joe ambling along, taking it easy. As I approached him I noticed he was sitting on the curb in front of a convenience store. His legs were draped out over a storm drain. I remember how weird and incongruous a sight it was. When I saw the whiteness of his face and heard his breathing, I knew something was wrong.

"Go call 911," I said to the lawyer.

"Dana, my chest is killing me. Oh, the pain! It's going into my arms. What is it?"

Joe got out that much history and lay back. His hands were like ice and he was diaphoretic. I felt his pulse and noticed skipped beats.

"My God, I've got to resuscitate him right here on the damn curb, with his legs sticking out into the traffic!" I thought.

The paramedics pulled up shortly thereafter. My stomach had long since leapt out of my abdomen and into my mouth. I was too amazed to feel panic, although a terrible fear was starting to rise up inside me. The paramedics told me they would not need to call in to the base station if I took over the case. We could load him up and go, a short five minutes to the local hospital.

"Okay," I managed to croak out through a parched throat. "I'll take responsibility. Give him some oxygen and check his blood pressure."

I gave him sublingual nitroglycerin and climbed into the back of the rig. I felt awkward and out of place in the confined ambulance, not knowing where anything was. They loaded him into the back with me. One of the paramedics came in while the other slammed shut the back door, then moved forward to the driver's side.

Joe went from sinus tachycardia into ventricular fibrillation with no warning. For a moment both the paramedic and I froze. "Holy Jesus," I yelled. "He's in V-fib!" The paramedic gave him a precordial thump. Joe started seizing. I grabbed for a mask, flailing in the back for an airway as the defibrillator charged. We shocked him once, he moaned, took a deep breath, and was back in sinus. "Joe, Joe . . . breathe. Come on!" Breathe he did, but on the way to the hospital he required defibrillation two more times. He was awake but groggy when we pulled into the emergency department.

A 12-lead electrocardiogram showed an acute anterior myocardial infarction. When the ER physician told Joe this, Joe said (with great comedic irony and sarcasm), "No kidding. I never would have guessed!" Then he asked for me.

Joe spent about a week in the hospital. Because of the dramatic and rapid intervention, he had what seemed like a complete recovery. He was under the care of a cardiologist and by six weeks had passed a treadmill test. He was going crazy sitting around the house and returned to jogging in the morning.

Over the next six months Joe made a few changes, like spending more time with his kids. He talked about getting out of the rat race and moving up to Oregon. I don't think he was serious. The heart attack became simply a bad memory. He didn't undergo any great spiritual or life-style transformation.

Two weeks before Joe's 40th birthday, we were out at the track. It was a Monday morning. Joe was looking forward to a hunting trip in Wyoming. As we came around a curve, he decided to walk a lap but said he felt fine. I continued on, ignoring the little voice in my head telling me to stick with him. He made it to the benches along the bleachers, those narrow, long, wooden, and low-set benches you see on the sidelines of every football field across America.

I didn't see Joe when he sat down, but the lawyer was with

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From the Department of Medicine, Division of Primary Care, Santa Clara Valley Medical Center, San Jose, California.
Reprint requests to Dana Frederick Hoch, MD, Department of Medicine, Division of Primary Care, Santa Clara Valley Medical Center, 751 S Bascom Ave, San Jose, CA 95128.

him. Joe said he felt a bit woozy and commented on the beauty of the approaching sunrise, the predawn sky and summer-like day we would have. Then he died.

I arrived and started CPR. I remember feeling resigned. Joe's respirations were stertorous, his jaws clenched shut, and the stare vacant and empty. This was so gruesome, bizarre, and surreal. Here we all were, in the still, gray light and the quiet just before sun-up. Yet here I was, again trying to resuscitate my friend, all alone in the hushed morning, a few kids and my other friends watching me. How long—10, 15 minutes? Finally the paramedics arrived.

"Let's put a board under him!" one said.

I nearly laughed. "What do you mean, he's on a board already!"

Once we got the monitor on, all we saw was fine ventricular fibrillation. Joe's arms draped down over the sides of the bench and flapped up, over, and across his body with each shock. I got him intubated, and we established intravenous access. Then I ran a code on a football field.

"Who's writing down the drugs?" I idiotically asked no one in particular, realizing this was no ER or CCU. This was my friend, not some anonymous person, dying in front of me.

After a few minutes more, we loaded him into the ambulance, and when we hit the same emergency department, the early day-shift nurses recognized me.

"Weren't you in here about six months ago?" one of them asked. "Some guy had an MI. A jogger. You resuscitated him?"

"Yep, that was me. I'm back. Same guy." I was now relieved. It was their scene, not mine anymore. Under the fluorescent lights, surrounded by the racks of IV bags, trauma equipment, and other gurneys, this all seemed as it should be. Later, I told Joe's family he was dead. For a while I felt guilty and responsible. With time, that has passed.

Because of my involvement in Joe's death, and life, I have been taught a lesson. Most of the patients in my practice are elderly and very sick. They talk mainly about the past: the many decades of ordinary days all strung together that make up a life. At this moment in my life, I, too, am focused on my own daily routine. My patients no longer have many options for future change. I assumed there would always be time to recast my life and head off on a new route if I wanted to. My friend's death gave an intense and emphatic notice that I can't take time for granted.

* * *

"Lessons From the Practice" presents a personal experience of practicing physicians, residents, and medical students that made a lasting impression on the author. These pieces will speak to the art of medicine and to the primary goals of medical practice—to heal and to care for others. Physicians interested in contributing to the series are encouraged to submit their "lessons" to the series' editors.

JONATHAN E. RODNICK, MD
STEPHEN J. McPHEE, MD
Series' Editors

Heart and Mind

MARSHALL H. CHIN, MD, *Boston, Massachusetts*

Internship was half over, and it was my first day on the General Medical Service—GMS, or "The Mess" as we affectionately called it. The GMS was universally feared as the most difficult rotation of internship—the most patients, the most admissions, and some of the sickest patients.

"And this is David," said my resident. "He'll be your patient."

"He's got a great family," chimed in the nurse.

I nodded and glanced at the sign-out: "Thirty-year-old man with chronic myelogenous leukemia. Now with blast crisis, fever, neutropenia. DNR."

We entered the room, and what I saw unnerved me. David was a ghost—sunken lifeless eyes, hollow ashen cheeks, ribs protruding with each labored breath, voice barely a whisper.

"Hi, I'm David's father." I turned, and a bear of a man greeted me with a warm smile and a firm, confident handshake.

"And I'm David's mother," calmly said a demure woman in the corner.

It was then that I noticed the fourth member of the family. Deep in thought, a young woman anxiously paced the room.

"I'm Doctor Chin."

"Oh, I'm Janet. David's wife."

Later that day, I reviewed the old chart. The medical record was a diary of pain—years of repeated chemotherapy, transfusions, infections, pneumonias, intubation, ICU, blast crisis, and now this final admission.

I walked into David's room. Again the father's checrful smile greeted me.

"The last few years must have been extremely difficult for your family," was all I could offer.

"Yes," affirmed the father as he assumed a grimmer tone and motioned towards the door. "David's a fighter, but the leukemia has taken its toll on all of us. We've been able to come to terms with it, however, and we're ready for death."

The father shifted his weight and paused for a moment. "The one I worry about, though, is Janet. She's seen him get progressively sicker. She knew this would eventually happen. But she hasn't been able to deal with it. Her mind knows the reality, but her heart can't accept it."

Over the next few days, Janet kept her mind busy by immersing herself in the details of David's care. She would page me at least two times a day to have me evaluate David or discuss his condition.

I soon developed a dichotomous approach to David's family. With his parents, I concentrated on discussing the process of dying; David's disease was horrendous, but death could at least be dignified or, strangely enough, even beautiful. I felt a natural bond with the parents.

With Janet, in contrast, I felt frustrated. Inevitably as she homed in on the details of David's care, I found myself discussing such topics as the benefits of one third-generation cephalosporin over another and whether 500 ml of urine output was an adequate response to 40 mg of furosemide. I just couldn't—or wouldn't—tell her what everyone knew: David was dying, and there was nothing we could do about it.

David continued his decline over the next few days. His lungs were a sponge for fluid, his blood counts continued to drop, and now he began coughing up blood. His family was incredibly devoted. Someone was with him at all hours of the day. I got into the habit of dropping into the room whenever I was on that particular floor, more to treat Janet than anything else.

The repeated bouts of coughing wore David down like the pummeling blows of a boxer. I looked at the resources in my armamentarium—100% oxygen face mask, bronchodilators, expectorants, antibiotics, diuretics, chest percussion, suction—all virtually useless. What I had left to give was my time, my ear, and, at least in Janet's case, the sense that 20th-century medicine, the big teaching hospital, and I were on David's side. The bottom line, though, was that David was dying in pain.

At this point, I wrote for David to receive IV morphine on an as-needed basis. I told David, his parents, and Janet that the morphine would be given only if the family requested it.

"But if morphine depresses his respiratory system, could this decrease his chances of clearing the secretions?" asked Janet.

Oh, how part of me longed to be brutally blunt. "Look, lady," I imagined myself saying to Janet, "Get a grip. The ballgame's over. He's dead!"

I put my white coat back on. I did not feel it was wise to burst Janet's bubble.

"Yes, it could. But he also needs to be kept comfortable," I answered.

Outside the room, the father came up to me visibly upset. "Of course he needs morphine!" he yelled. "This is getting ridiculous. She's getting out of hand."

"If you all can't agree on what to do about the morphine," I stated with a strong, steady voice, "I'll make a decision based on the medical facts." The tension on the father's face instantly melted, and he grunted his approval. I was never called on to make that decision.

Then, a strange silence developed. Janet stopped paging me. Also, as my service became busier, I checked on David less frequently.

I bumped into Janet later that week. "Do you think if I

(Chin MH: Heart and mind. West J Med 1991 Nov; 155:553-554)

Dr Chin is a medical resident at the Brigham and Women's Hospital, Boston, Massachusetts.
Reprint requests to Marshall H. Chin, MD, Department of Medicine, Brigham and Women's Hospital, 75 Francis St, Boston, MA 02115.

massaged his sides it would help him cough up the mucus?" she asked with bowed head.

I looked at her, and her eyes met mine.

"I mean, I was just wondering. . . ."

I nodded. We didn't need to say anything more.

The possibilities were endless. Perhaps my repeated warnings on the severity of David's condition had had their desired effect. Maybe David's father had taken Janet aside and told her to face reality. Maybe David had said good-bye to Janet. Maybe Janet had developed the strength to look the situation squarely in the eye, or just maybe Janet's final defense mechanisms had been overwhelmed and all her emotions were starting to tumble forth. I'll probably never know what caused this gradual transformation in Janet.

Finally one morning I encountered what every pre-rounding intern dreads—the empty bed. I sought out the nurse.

"He died peacefully. His parents were with him at the time of his death. They were relieved."

"And Janet?"

"She arrived just after he died."

I got a call from David's hematologist that day. The family had expressed their appreciation to the medical team for its efforts and understanding.

Still, something gnawed at me.

I picked up the phone later that day and dialed.

"Hello." David's father had answered the phone.

"Hi, this is Marshall Chin. Is Janet there?"

"Wait a minute."

As soon as Janet got on the line, I sensed the difference. The words flowed easily as she described her sadness and frustration. Matter-of-factly she stated that she must have been difficult to work with. She, too, thanked me for my efforts. The tension had dropped from her voice. She was a free woman.

I hung up the phone.

My heart and mind were one again.

* * *

"Lessons From the Practice" presents a personal experience of practicing physicians, residents, and medical students that made a lasting impression on the author. These pieces will speak to the art of medicine and to the primary goals of medical practice—to heal and to care for others. Physicians interested in contributing to the series are encouraged to submit their "lessons" to the series' editors.

JONATHAN E. RODNICK, MD
STEPHEN J. McPHEE, MD
Series' Editors

Special Article

Memoirs of an Amnesiac—Two Years With Brain Cancer, or the Outer Space of Living With Brain Tumors

ALEXANDRA DANE DOR-NER

Alexandra Dane Dor-Ner ("Ali" to friends) was a photographer, writer, and a producer of programs on child development. In February 1989, at the age of 41, she was diagnosed with malignant brain cancer. During the following months she underwent brain surgery, radiation, and implant radiation. Throughout her treatment, she continued to work on a novel and write stories and literary criticism. A volunteer in hospitals before her illness, she now became very active in a support group of brain tumor patients and often served as a first resource and contact for others diagnosed with brain cancer. Ali was very accomplished; her award-winning photographs have been exhibited in the Smithsonian Institution in Washington, and her articles and pictures were published in books, periodicals, and newspapers around the world. A native of Boston, Ali lived for 17 years in Israel, where she joined a group of photographers documenting disappearing neighborhoods in Jerusalem. She was awarded first prize in the "Israel Through the Camera's Eye" competition in 1977. She also taught English and photography in Israeli high schools. Ali traveled extensively on photographic assignments. Early in their 22-year marriage, she and her husband circumnavigated the globe on a freighter, producing a documentary film of the voyage. "Memoirs of an Amnesiac" was written while Ali was a student at the Warren Wilson College Writers' Program in North Carolina; she intended to explore the compensatory aspects of her disease. In February 1991, within days of completing the piece, Ali had a third brain operation to remove a regrowth of cancerous tumor cells, as well as necrotic tissue. Two days later, she was again operated on to remove blood clots resulting from the previous surgery. For the next 12 weeks she fought to regain her ability to walk, talk, and write. In May, she underwent a fifth operation to relieve pressure in the brain. She was still in the hospital when she learned, to her great pleasure, that she would be awarded a master of fine arts degree from Warren Wilson College. She died on June 19, 1991.

HELEN FREMONT
Cambridge, Massachusetts

(Dor-Ner AD: Memoirs of an amnesiac—Two years with brain cancer, or the outer space of living with brain tumors. West J Med 1991 Nov; 155: 555-560)

- *Before Getting Sick: An Imbalance of Ease*

MAYBE WHY I got it in the first place: I had too many breaks before. My life until the age of 41 had only the merest difficulties, an imbalance of ease, an affluent fluidity, where trusting parents drew up trust funds every time they sat down. I wouldn't call it blessed, but there was little to complain about. I told my husband in the early days of the diagnosis that if I were to die soon, I would be sad for the sake of my kids and for him, but not in terms of my own life. I had not missed out on many things. I've traveled around the world, left my own culture to become part of another, married a fascinating man at the foolish age of 21. Our marriage, now 21 years old, has been a mutual effort but well worth it. I have two daughters who have given me more moments of joy and being than anything on earth. All of this I had before I was threatened. Since then, I have met many patients who are alone, scared and bitter, whose friends have backed off, and in some cases, even spouses; and their tumors are many times more wicked than mine.

- *The Tumor Itself: My Head, the Scar, Sewing, the All-Purpose Fishing Knot*

As unlucky as I was to get the tumor in the first place, the luck of various aspects of it couldn't be denied. Its placement was very close to the surface, in what the doctors call the noneloquent section of the brain. Even learning that term thrilled me. I guess what I like about brain cancer is the knowledge you learn about your brain; it is impossible not to learn more about the mind. Noneloquent sections of the brain—the obvious next questions are, What and where are the eloquent sections? And what doctor ever named these parts this way? At first I understood it all to mean that everyone assumed I was right-handed and my left hand, only, had been injured, not too badly. But as I read books, especially *The Man Who Mistook His Wife for a Hat* by Oliver Sacks, I learned that the right frontal lobe is called the noneloquent area (as is about 80% of the rest of the brain), more because of scientists' lack of eloquence about *it* than because of the brain's characteristics. This large area is one that no one understands the use of. I am not sure I accept the idea that the brain has such large useless appendices, just as I never really accepted my smiling neurosurgeon's argument that since I'd come through the craniotomy so well, radiation would impose no risk. I felt every time they did anything to my brain, I was pushing my luck. If you read Sacks's *The Man Who Mistook His Wife for a Hat,* you see that damage to the right frontal lobe causes subtle deficits, and in looking at them you are forced to consider the otherwise normal-and-taken-for-granted brain functions. The cases in Sacks's book are mostly about right frontal lobe problems.

Had my anaplastic astrocytoma taken root just 15 mm to the left, I would not be writing this today. So depth, site, and type of cell were my compensations. My astrocytomas are grade three on the scale of four, four being the highest level of

malignancy, the mega-maligno-monsters. Glioblastomas. Two young women who were friends for less than six months, from brain tumor support groups, have already died of these tumors. The malignancy rate is measured by how quickly and how large a percentage of the cells are dividing, their "mitotic rate."

My cancer cells do have one trait that is not so lucky—they are shooting stars of disease. They have the ability to travel and tend to. These star-shaped cells are not the quick triangular kind of stars that we all proudly learned to draw as children. My cells have no straight lines, just curving half-moon shapes around a large middle—a body and prongs—explosions of cellular life. To me, they look, ironically, very like brain neuron cells. "Anaplastic" means they are polymorphic, changing their original star shape to match where they land.

When my bandages came off, I couldn't believe the neatness of my stitches. I felt my surgeon's sewing up was an indication of how neatly he had worked inside, and at our last meeting I told him so. By then, though, I had read a book about neurosurgeons that implied they never sewed up on the difficult operations but left that to lesser-high-ups. My surgeon insisted he had done everything and walked out of the room proudly, hugging the huge clay pot of blooming tulips my family had gotten for him.

At a later date, another doctor was stitching up drill holes in my head, in my hospital room, no anesthesia; it wasn't supposed to hurt that much. My husband was with me, though. The anesthesia of holding his hand always works for me. I was nervous until he said, "Ali, guess what kind of knot Dr Alexander uses?"

"I give up. You tell me."

"The same fishing knot you use."

This all-purpose fishing knot consists of a loop with the extra edge wrapped around the base six times and then pulled tight. An easy-to-do knot. When I do it, I always spit on the loops, to reduce friction. Dr Alexander eliminated the spitting part. He said, "Oh, Ali, do you fish?"

"Yes, let me tell you about the big one that didn't get away."

I described my foot-and-a-half-long bluefish that stopped our sailboat dead in the water. The fish was so heavy that Zvi had to haul him aboard.

Just telling the doctor about those healthier, glorious times took my mind away from my head, and nothing he did was painful. Maybe the medical profession should look into patient pride as a powerful anesthetic. Bragging takes energy and protects. If I knew I would be praised after each gruesome procedure, I would probably be willing to be more brave.

- *Other Means of Coping*

My favorite, as-yet-untried, Polish joke for appointments with doctors is: How many astrocytes does it take to turn on a tumor? I have been too shy to ask it. Denial, though it has served me very well for the last year, is frowned upon by most of the medical profession. "Patient has an unreal sense of the future, no comprehension of the severity of her own situation." I am sure this has been written in my chart. It is only partially true—I don't know everything, and my nightmares are as graphic as any. I have learned as much as I can, but I have also learned that humor is as great a weapon as denial. In the beginning, my denial was so strong I couldn't deny it. I'd rank my defenses, my Star Wars, as: radiation, denial, humor, and gathering information. Nowadays my favorite books are about neurology and cancer. I have always found medicine fascinating; this is probably as close as I will ever come to being able to indulge my craving for reading medical books.

I know also that hiding behind medical facts is a very common way for people to deal with frightening medical situations. Doctors and nurses in the NICU (Neonatal Intensive Care Unit) know that at least one parent of a very premature baby will become the expert in the baby's problems, learning to talk like a third-year resident. While one parent weeps, unable to speak, the other might be rattling off questions about the baby's blood gases and whether extubation will happen this week or next.

I am not an expert but an admirer of the complexity of the brain. In the very beginning I was sent two kinds of books by friends: The story of other peoples' tumors—tumor tales—and New Age cure-yourself-by-good-thoughts books, like Bernie Segal's. His books, though filled with success stories, made me feel guilty and convinced me that if I didn't get better it would be my own fault. The case histories depressed me, too, because I knew that my personality was the unhealthy "people-pleaser" type. I immediately had everyone else's symptoms, painful therapies, and tests, as well as my own. But I was grateful for every book. Reading was, and is, the best escape—a horizontal activity that can be slipped out of, into sleep, with no one knowing.

Reading also meant catching the gist, the best, of every subject or person, without sifting through nervousness and blather. It was having a conversation with someone intelligent enough to write a book without having to put up with eyes full of pity. I could skip passages, cry by myself, stop and start again. There's a freedom and privacy to reading that in-person hospital visits don't allow.

Some of my visitors grasped whatever railing there was at the foot of the bed and wept. I hadn't even wept yet and felt they were behaving poorly. They might stay there for a few minutes, just weeping at me. What was I supposed to say? How was I supposed to comfort them? I know I look bad, or different, but don't worry, it'll be all right, don't cry?

- *What I've Learned About Friendship*

Friends and how to be one—to someone who is sick. I am often asked what was the most helpful approach. As much as I have learned about brain cancer, I have learned about people I thought I knew very well. One thing was true for all of my women friends: they taught me how to be a friend and what friendship should mean in a time of distress. I learned from my friends how to take care of friends. It was very embarrassing to realize that I had never been so generous to any friend as they were all being to me.

I am often asked now, what is the best way to be when visiting a friend with cancer or in a situation like mine. Be interesting. If you can, be funny. Be willing to listen if the person wants to tell about the horrors of it, but don't assume they do. I think of the opening in the Amy Hempel story, "The Cemetery Where Al Jolson Is Buried" from her collection *Reasons for Living*, where the sick friend asks her healthy visitor for fascinating but trivial bits of information. I hate to say it, but gossip is a great topic. Be the talker, let the patient listen or talk if she wants to, but don't leave the brunt of the conversation on her. Leave her room five minutes

before you want to. There were certain visitors I had whom I felt I had to entertain, since they were rendered speechless by the look of the room and of me.

• *Family Reactions*

I had one week—between my first life-saving, or eloquent, seizures, which alerted me and the doctors to the fact that I had a moderately fast-growing tumor, the size of a man's fist, in the spaceless area between my skull and brain—and my craniotomy to remove it. I was sent home to rest. The first day home from the hospital, I thought it would be a week of torture. Physically, I didn't feel bad. Emotionally, I was very scared of the craniotomy. What if I woke up and didn't know myself or my children?

I thought I would pass the waiting week like a prisoner on death row, knowing that on a certain date I might leave this life. But because of one of the medicines I was still on, steroids, to keep any brain swelling down, I was quite high—not confident but in very good spirits—and because I was high my family was, too. That made for a wonderful week. And because my best/best friend took time off from work so she could have lunch with me every day, I was high.

Two days before the operation, I decided my daughters and I would all go to the hairdressers. They needed trims, and I thought I was probably healthier and stronger at that time than I would be in the weeks to follow. More truthfully, and more selfishly, I wanted to get a haircut. Since I would be shaved for the operation and lose the rest of my hair in radiation, I thought it was a consequenceless chance to experiment with an extremely short cut. We had a great time, except for the animosity of the young man who cut my hair. He'd ask if I wanted it this way, or that, and I kept answering, "I don't really care," and that it didn't matter. His professional ego was not stroked. When I told him why I didn't care, he was disgusted and behaved as if what I had was contagious and he could get it by standing too close to my head. He was dressed entirely in black and when he stood about two feet away from my chair and bent over to cut my hair he looked like an acrobat performing the letter "n." From his neck hung a golden star of David that swung and caught the light. He mumbled to himself in Hebrew; I didn't let on that I understood what he was saying about these crazy unfashionable American women who spent money on themselves but had no sense of style and didn't really care how they looked.

When we were all done, my girls, skipping ahead of me down the sidewalk, looked so neat and well groomed—like someone else's children. And I had a cut I knew why I'd avoided all these years. My sister comforted me with compliments about the attractive shape of my head. I felt so good about the girls' haircuts, maybe the way an animal mother feels after a good grooming of cubs. The girls seemed happy, too. They knew I was going into the hospital the next day, for a week, and I think they were very satisfied to have this much attention paid to them just before. They didn't understand, though, why I didn't want to spend the rest of the day going through their closets with them, making lists for summer and spring shopping. I don't remember what I did for the rest of the day, but whatever it was, there was plenty of stroking of my own head, running my fingers through the fuzzy shortness of it. And the scarlessness. My sister was right, I saw when I could bear to look at myself in the mirror: my head had a classic pretty shape.

My two sisters were spending most of their time with me, neatening my desk, installing paring knives and potato peelers in every kitchen drawer, since whenever they couldn't find one they assumed I didn't own one.

I now remember that before I got sick (hard to know what words to use, since I never really had any symptoms before I found out what I had), the one distressing change I'd noticed over the past weeks was a creeping disorder in my mind that was mirrored on my desk and in my closet and kitchen. But since I've always been messy, it was hard to sense if things were getting worse or if I was just getting tired of myself. I would have fantasies of my older, neater sisters swooping in to set things straight.

So that week was a surprisingly calm family time with plenty of long night talks with my sisters who both have families of their own and who I never get to see enough. My brother Jack, 15 months younger than I and therefore an inseparable playmate when we were children, called almost every day to see if I'd started to ask, "Why me?" I hadn't, and knew from the frightened strain in his voice that he was asking himself, "Why her and will I be next?" He always wanted to know if I had any idea why I'd gotten brain cancer or how long I had it. Questions I had no answer to.

My daughters never asked me anything and rarely volunteered their fears or doubts. Daphne's birthday was three days after the craniotomy, and she was more worried about missing her birthday party than about me, but I figured that was normal. I got home in time for the party but by now have no recollection what we did for her. I do remember, though, coming home and fighting with Tamar, because she wouldn't run an errand for me. Just before I was about to let loose a slingshot full of, "How could you? You selfish little bitch! Do you know what I've gone through?" I stopped and realized that in her own 11-year-old way she was showing me that she had come through this unscathed. I was, when I could remember to count to ten before reacting, happy that she wouldn't wait on me hand and foot. Daphne, at nine, would worry, and even with her speechlessness I knew, because she stayed very close, curling up by my side when I slept, and kissing my bare forearm at 15-minute intervals. I thought of them as thermometer kisses. She seemed to be checking my life warmth. My husband, Zvi, had a very important business trip coming up where he had to sail on a Venezuelan Navy training boat along the coast of Cuba. It was going to be rough accommodations and rough sailing. He kept asking if I was ready to travel yet. I finally communicated clearly that even if I was, I didn't want to. Could he go then? Was it really OK? Yes, of course. I could be generous when the alternative was going with him. But as his departure date drew near, he became sadder and more anxious. One day, quite rare tears flooded his eyes and he said, "I know that I can get away from this horrible thing that has happened to you, by traveling. I know that under the pressures of work, I will forget—but I guess I know, too, that you can never forget it, or escape it." I said that was true. But I am happy to say, now, that there are definitely stretches of time when I do forget. But I have to keep a watchful eye on the forgetting. If I start feeling too healthy, I skip my seizure-prevention medications and then I get reminded with a wallop.

• *Seizures*

There is nothing like a grand mal breakthrough, with no aura to warn me of its coming, to remind me that the "cured" brain cancer patient is not home free. "Breakthrough"

means that the seizure activity has occurred despite the sedatives prescribed to quiet the electrical activity of the brain. The trade-off in brain cancer is that even if they succeed in eradicating the cancer, the cost is a lifelong epilepsy where the immediate causes of the seizures are known but cannot be cured. The scars on the brain from the various therapies are focal points for seizures, but nobody really knows why they happen at some times and not others.

I have had four breakthrough seizures. The only steadfast rule is: No Sleep Deprivation. So I rigorously enforce my daily nap and try to take care of myself. "Get plenty of sleep," my doctors say. How can I fail to, taking 390 mg of sedatives a day? My definition of sleep deprivation was the one left over from a younger, healthier self, with the consecutive sleepless nights of crying babies born 18 months apart. It is hard to accept that now it means missing my afternoon nap.

• *Recuperation*

Waking up from general anesthesia, after the operation, was one of the worst feelings in the world. I was nauseous, disoriented, and terribly anxious that a headache might be lying in wait, ready to ambush me if I turned my head too quickly or tried to sit up. A big bandage was wrapped around my head. All I wanted was to hug my middle sister Gretchen, who with her ferocious optimism always refused to hear my complaints. I wanted her telling me that I would feel better in time, but I also wanted to tell her that all I wished to do at that moment was die. That feeling quickly passed. She would have been right; there is nothing like the human body recuperating and general anesthesia wearing off. If any religious person had told me it was God's work, I'd have been converted.

• *Changes*

I am extremely nearsighted and had stopped wearing contact lenses since the first seizure—it seemed a vain nuisance. But after the operation, with the bandages and swelling, there was nowhere to stick my glasses behind my ears. The cut had started from the highest point of my right ear across the top of my head almost all the way to the left ear. Also, since there was swelling, the glasses fitted to a pre-operation head were uncomfortable. I took one or two of my first walks without glasses. Neurology patients were on one of the pod-shaped sections of the 12th floor; the other identical pod was for cardiac patients. Who decides such things? I would go round and round the pods. It was on my first day that I got very scared. Finally, as if thrown by centrifugal force, I left my pod and went down a long corridor to the "heart pod." When I arrived back at my own pod, I realized I didn't know my own room number. It seemed highly embarrassing to have to ask one of the nurses which room was mine. Without my glasses, I had to enter each room to see if my posters were on the walls.

After that I found walks without my glasses were quite feasible. When I didn't go to the cardiac pod, I'd walk to the large windows by the elevators. Holding my glasses to my face, I'd look across the roof tops until I was sure I'd spotted my apartment. Whatever time of day it was, I tried to imagine the life going on there without me. Then, turning, I could watch the elevators discharge their loads of visitors. Each group stepped gingerly out, as though they were leaving a dinghy for shore and they were still over rocky wavy water and they had worn the wrong shoes. "What are you afraid of?" I wanted to ask. But one look at me and all they would have to do is point. While I stood by the elevators, I hoped my own family would emerge so I could show them how well I was doing.

The more walks I took without my glasses, the freer I felt, and finding them was no longer a necessary prerequisite for leaving my room. Maybe I smiled at a few cardiac patients I didn't know, and perhaps I snubbed some of my own nurses, but I'm sure I missed a lot of the looks I would be getting for months, those "Who is that tall lady with the strange things going on with her head?" "Who's that freak?" looks. The walk was so effortless in terms of sight that I began to dream that the surgery somehow corrected my shortsightedness. I race-walked back to my room to find my glasses and experiment. No, the glasses still did improve my vision, but I had no desire to wear them when my whole head was swollen and the glasses fit too tightly. As the days went by, I found I got used to not wearing them, to not seeing well, and since there had been no other effect of the operation, I almost felt justified in not having perfect vision.

Later, when I was home and went for walks outside, I preferred not to see the expressions on people's faces as they saw me. By that time I had no bandages, and also no hair, as it had been shaved off in two directions and lengths. From the scar to the back of my neck, my hair was cut to about half an inch; from the scar forward, it was a marine recruit's stubble. As it turned out, this didn't matter, because radiation therapy made all my hair fall out anyway, in strange patterns and at differing times.

What was the compensation for this trivial feminine-fashion aspect of brain cancer? I finally got rid of a terrible perm that had ruined my hair and that could only possibly have been remedied by another perm that I had been unwilling to have. I saved at least 20 minutes every morning and evening by not having hair. Not having to worry about how I looked was refreshing. I looked weird and there was nothing I could do or had to do. I had a valid reason to look that way. Emerson has a quote about adversity sometimes freeing us from the terrible bonds of vanity. I definitely had that compensation, a mixed blessing.

I gained about 30 lb and couldn't wear any of my old clothes but could not accept the new me long enough to shop for it. I grew a new figure. At night I felt as though some other woman was getting into bed with me: a stranger with breasts and hips and flab. For a while I wore my husband's jeans, something I hadn't done since I was pregnant. At the same time I realized I could give my now-too-small bras to my oldest daughter. They fit her perfectly. I wondered if there was some strange justice to these clothing transfers made necessary by the changes in my body. Perhaps the same justice that had my youngest daughter worrying about the celebration of her birthday while I was wondering how many more I was going to be allowed to celebrate.

• *Lies*

Lies, "bovine scatology," as General Norman Schwartzkopf would say. For three hours yesterday morning, I blushed for every brave-sounding word I'd written here. All it took was a phone call to my neurosurgeon's office, to verify the time of my appointment that day, and to have his secretary tell me it was great I called because they wanted me to come in early. My doctor had scheduled another scan for me at noon. A technetium-thallium scan.

Now, I know these scans. They have a very distinct hierarchy, almost like the ASA ratings of photographic films. My regular every-two-month scan is a dye-injection CT (computed tomography) scan. Technetium-thallium scans are done only when there is something baffling on the CT scan. Anything that baffles my docs does not please me or them. It means that there is a disagreement about the interpretation. What one doctor sees as dead tissue resulting from radiation therapy, another sees as possible new tumor growth. All of this comes out as a white area on the scan. It is all called "enhancement." In the early days I thought my tumor areas had taken to wearing eye shadow.

Anyway, the minute this woman said that a tech-thall scan had been scheduled, I leapt to my own conclusions: my CT scan on Saturday had been bad, and they needed quick verification. They were worried. I was scared shitless (forgive but don't forget my language). My knees were knocking. I felt like weeping, losing control, but realized that I didn't really know anything for sure. I wanted to call all my friends but refrained from doing so. They would rush to the hospital, or worry, and then when this whole business was over, I knew I would be exhausted and I would have to explain and call back.

So I paced, waited for my husband to arrive to take me to the hospital, and, as I said, contemplated wiping out this whole compensatory hogwash.

There is no compensation. Just, if you work very hard, a few redeeming moments, great family time and appreciation, marital peaks. I received many compliments for the way I went through this ordeal the first time around. I guess the shameful secret that only I know is, the second time around I don't see how I can be so nice. Even during the tech-thall scan, an hour-long scan where you must lie stone still or they start over. And then there is the business of injections, first one of thallium, which goes to the tumor cells, either they like it or it likes them, how the hell should I know? By the way, check all the science in this, I feel it's unfair that I should be expected to learn all this crap *and* be sick. Technetium is another radioactive element that shows up in the blood supply to the brain—if the new enhancement is tumor, it needs blood.

Veins. Mine have been maligned at every turn. "Oh, watch out for her, she has bad veins," or weak veins, or some such thing. Any time a blood-drawing nurse comes close to me, I tell them, "Three strikes and you are out." No more digging around in my arm with needles. I am not a pincushion nor will I become a pinhead.

One of my sweetest doctors just called, my old radiologist who is not treating me right now, but who, according to everyone, is really involved in my case. He had seen the tech-thall scan, and, after much covering of his own tail, since he convinced me to go through an extremely painful radiation implant in my brain shortly after my first craniotomy, he told me that he had seen the new scan and that it showed an area that should be examined. He said my neurosurgeon would probably be suggesting another operation to get rid of the dead tissue from all the old radiation, which will cause me problems some day if it hasn't already. It has, headaches so bad last summer that I called the surgeon and asked for the operation to remove the necrotic tumor tissue, but the surgeon said to wait. The radiologist went on to say that when the neurosurgeon opened me up this time, they would remove some of the new stuff, the "enhancement" on the new scan, and send it to pathology to see what it is. If it's cancerous, and I guess I already assume it is, I mean it can't be gold, or the cure to AIDS, right? then I will probably have some super-high-beam radiation to exactly that spot, since my brain as a whole has already received the maximum amount of radiation it can take.

All of this should happen fairly soon, within a month, he said, we should not wait for the summer. That suits me, since I want to go ahead with submitting my petition to graduate from the MFA Program for Writers at Warren Wilson College, which is due March 1st, and to keep the goal of graduating in July. I think this plan is feasible. I am not, at the moment, telling the program director about this. I don't want special treatment just yet, since I haven't even heard from my doctor what's up. The operation date has been set for February 27th. Don't worry, this is not life-threatening since we know about it and will act on it.

OK, back to being a goody-goody.

What has this experience given me? Experience, fear, dread, pain, and something to write about. So compensatory becomes cum-pen-satory.

Similar to a broken heart, it seems, shattered health leads to confessional surges. Remember that *Life Magazine* picture of President Lyndon Johnson showing his scars? I always liked the man more for that, but I know it didn't go over well with the general public.

This is now even more difficult to write, since I have destroyed my organizing thread. An essay on the compensations of illness minus the idea of compensation is not very coherent. Maybe after next month's hospital experience, I'll find another handle. Can I write on and on for eight pages and then refute everything I have said? Why will anyone believe me from there on. OK. Truth and reader belief aren't everything, but I am beginning to feel very foolish. This remains something I want to write with the lights out and have it read that way, too. I find within this nonfiction mode, I lose the flow of writing/language. I am always backing myself into corners with passive constructions and godzillions of gerunds in participial phrases. Grammar has become like hurdles in a track event, every thought requiring great effort to express. I know it is because I am trying to pack in the facts, but the facts are what make it interesting, them and the details. This new version is not better than the last; in fact, it has moved miles away from being anything completed.

I don't feel any margin red stars, and I crave red stars or gold—second grader that I am. I now know that I write for margin compliments and the relief of sorting out the events of my life, discovering what can only be discovered when writing. But let's be really honest because anything else gives me a headache: I write for compliments in the margin, that's what keeps me going, and wanting to go on.

- *Worse Than the Disease Itself: Calling the Doctor*

They always say, Let's do this test, or scan, and you call me in a few hours, and I'll tell you what we found. What they don't say is that in a few hours they will have picked up six new acute cases, and they won't have had time to look at the scan. But I still reach them at the original time, and they are apologetic and say, Try me in another hour—and that goes on all afternoon, until nightfall, and they go home. Of course, during the night I can have them paged. The page operator says sweetly, "Outside the hospital, page calls are emergency only," and then shouts, "IS THIS AN EMERGENCY?"

"Well, it is information that I am dying to know, but I am not dying."

"WELL, MA'AM, SORRY, BUT I CAN'T PAGE HIM."

Then my husband shouts and says, "You are an emergency, and I want them during the operation to do a biopsy, not an autopsy, so what's wrong with lying?"

A continuous debate between us. He always gets faster medical attention than I do because I am a female wimp who never believes she should really be taking up the doctor's time. *My* bravery amounts to withstanding a whole lot of pain, as long as I don't have to disturb a doctor, knock on a closed door, call him at home on a holiday. I know this is sick, and in the last two years I have become mildly more assertive. I suppose it is nice that I can still laugh at myself.

In writing all of this, I want to do justice to what my head has gone through. This horrid experience has been an experience, the tumor is, maybe, a gift of meaning to my life and to what I want to write. The dreadful irony is that this Indian giver may some day take away any ability of mine to understand meaning.

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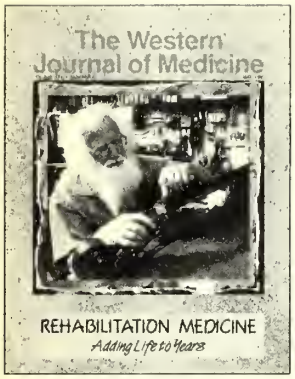

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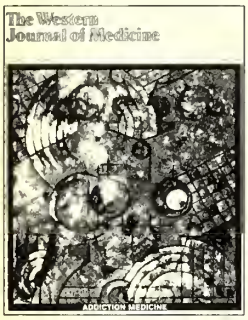
- HIV INFECTION: IMPLICATIONS FOR REHABILITATION MEDICINE *Jon A. Mukand*
- PAIN CENTERS: ORGANIZATION AND OUTCOME *Sridhar V. Vasudevan and N. Timothy Lynch*
- USE IT OR LOSE IT: THE HAZARDS OF BED REST AND INACTIVITY *Paul J. Corcoran*
- CEREBRAL PALSY *Gabriella E. Molnar*
- REVERSING DISABILITY OF IRREVERSIBLE LUNG DISEASE *Brian L. Tiep*
- SEX AND DISABILITY ARE NOT MUTUALLY EXCLUSIVE *George Szasz*
- WORKER REHABILITATION PROGRAMS: SEPARATING FACT FROM FICTION *Andrew J. Haig and Suzanne Penha*



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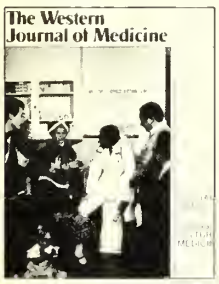

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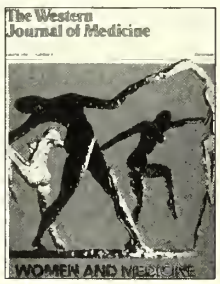

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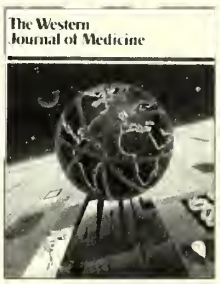

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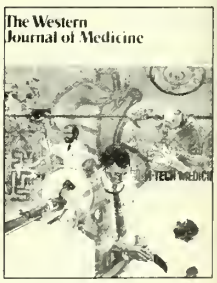

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Books

3. Berne EJ: Role playing in therapy, chap 2, Principles of Group Therapy. New York, NY, Oxford University Press, 1966, pp 35-51 (author of book is same as author of chapter)
4. Munsung JD: The role of drugs, chap 2, *In* Brest AN, Mayer JD (Eds): Hypertension—Vol 3, Therapy, 2nd Ed. Chicago, Ill, Year Book Medical Publishers, 1961, pp 456-479 (authors of book differ from chapter author)

Correspondence

5. Shusterman D: Espresso maker's wrist (Correspondence). West J Med 1990; 152:721-722

Government Publications

6. The Health Consequences of Smoking—Cardiovascular Disease: A Report of the Surgeon General. Washington, DC, US Dept of Health and Human Services publication No. (PHS) 84-50204, 1983
7. Centers for Disease Control: Update: Acquired immunodeficiency syndrome—United States. MMWR 1987; 36:522-526

Proceedings

8. O'Connell M: A Controlled Trial of Regional Intra-arterial FUDR Versus Systemic 5FU for the Treatment of Metastatic Colorectal Cancer Confined to the Liver. Presented at the annual meeting of the American Society of Clinical Oncology, San Francisco, December 1989

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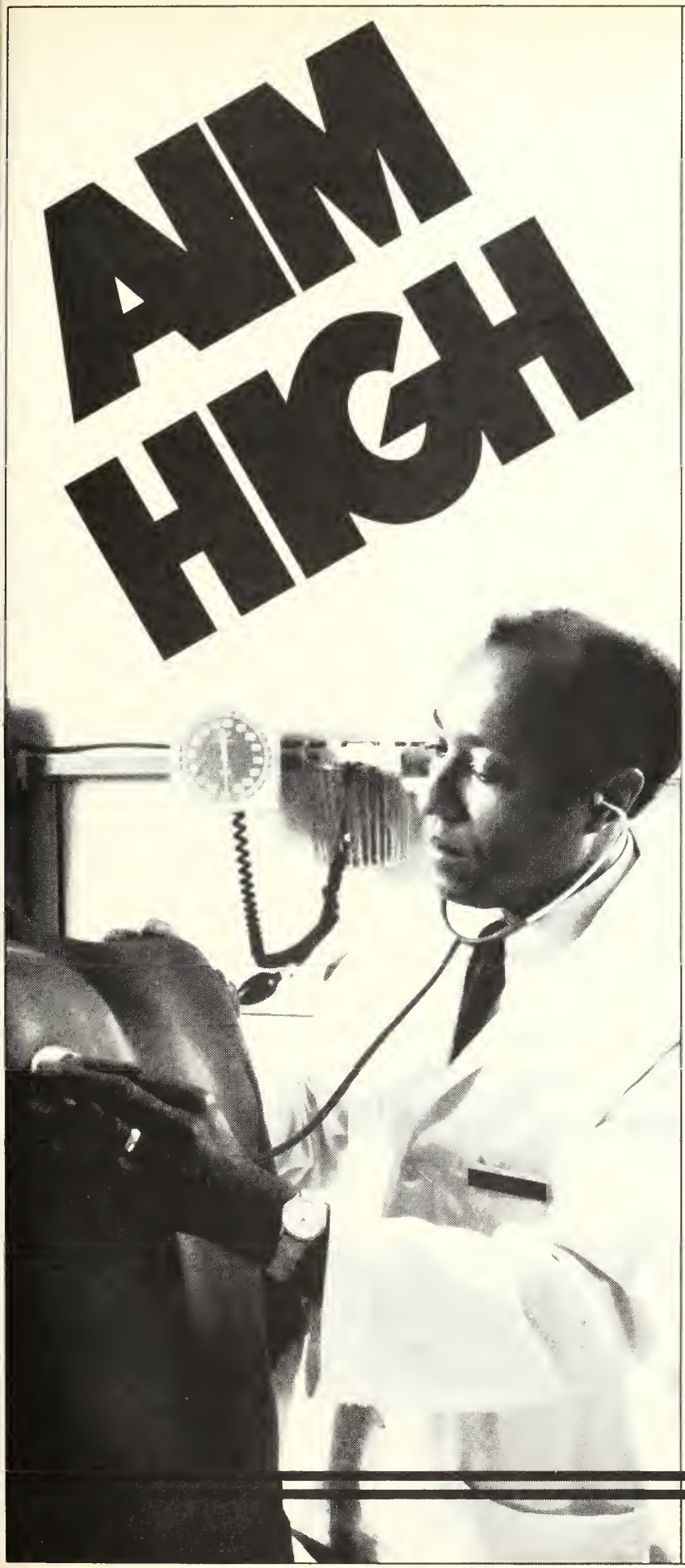

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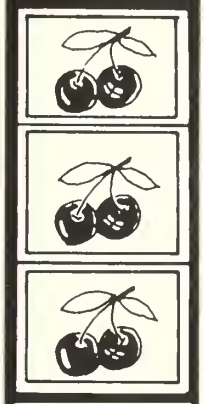

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(Continued on Page 568)

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(Continued from Page 567)

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CALIFORNIA. Physician Recruiting Services available to solo practitioners, single and multispecialty clinics, and hospitals. Placement positions available in Invasive Cardiology, Family Practice, Dermatology, Internal Medicine, OB/GYN, Orthopedic Surgery, Neurology, General (Vascular) Surgery, Pediatrics, Urology, and others. For information call Bradshaw Associates, 21 Altamount, Orinda, CA 94563; (510) 376-0762.

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CALIFORNIA MEDICAL/LEGAL DISABILITY EVALUATIONS. Opportunities available in San Jose, San Ramon, Fremont, and Capitola, California for BC physicians in Orthopedics, Psychiatry, and Cardiology with multispecialty forensic medical evaluation group. Practice limited to evaluations. California license required. Excellent opportunity to supplement income. Send inquiry and CV to Martie Woodson, QMA, 2131 The Alameda, San Jose, CA 95126.

FAMILY PRACTITIONER, Solvang, California, 30 miles north of Santa Barbara in beautiful Santa Ynez Valley. Opportunity available to join three other Family Practitioners in a wonderful practice. Call (805) 688-3440. Drs Alan Hersh, Robert Gottesman.

NORTHERN CALIFORNIA—LOS GATOS. Medical group of four seeking Family Physician to replace physician leaving. Full-time, Monday through Friday. Share call with six other physicians. Close to Good Samaritan Hospital. Full lab and x-ray in office. Contact Teri Daniels; (408) 377-9180.

FAMILY PRACTICE—SEATTLE, WASHINGTON AREA. Group of three Family Practitioners are seeking a fourth physician. Must do Obstetrics. Excellent practice. Young physicians. For details, call Eloise Gusman, (800) 535-7698 or send CV to PO Box 101656, Fort Worth, TX 76109.

PEDIATRICIAN BC/BE for hospital-based teaching practice. Interest and training in Neonatology and Critical Care Pediatrics preferred. Join three full-time Pediatricians and two full-time Neonatologists in hospital with Community Level III NICN and busy inpatient and outpatient services. Paid malpractice. Salary negotiable based on training and experience. Submit CV and references to Leedell Reuben, MD, Director, Pediatrics/Neonatal Services, San Joaquin General Hospital, PO Box 1020, Stockton, CA 95201, (209) 468-6611. AA/EOE.

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Many multispecialty groups and hospitals have asked us to recruit for over 300 positions of various specialties. Both permanent and locum tenens. Send CV to **Western States Physician Services, 5627 E. Kings Canyon, Ste 156, Fresno, CA 93727, or call 1 (800) 873-0786.**

EMERGENCY MEDICINE, New Mexico—Albuquerque. 14 physician group covering three hospitals. Must be BC/BE in Emergency Medicine. Competitive salary and benefits for region. Moderate volume and acuity. Excellent recreation and weather. Send CV to Medical Director, Emergency Department, 601 Grand NE, Albuquerque, NM 87102; or call (505) 848-8134.

SOUTHERN CALIFORNIA COASTAL COMMUNITY CARDIOLOGIST: BC/BE—invasive with angioplasty experience a requirement. Emergency Physician capability preferred—to join four person Cardiology group July '92. All members are BC, one invasive, three noninvasive. Please forward CV to Number 248, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

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A MULTISPECIALTY GROUP IN SAN JOSE, CALIFORNIA SEEKS A BC/BE INTERNIST to join their busy Internal Medicine department of seven Internists. Call schedule will be 1:8. Competitive salary and benefits offered. Call Jan Sturges at (408) 999-7110 or send CV to MMS, 532 Race St, San Jose, CA 95126-3432.

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INTERNIST/FAMILY PRACTITIONER—Northern California. Immediate opportunity for BC/BE Internal Medicine/Family Practice. Practice associate emphasized or solo practice. Located north of San Francisco in wine country with outdoor activities. Assistance available for relocation and establishment of practice. Contact Margaret Ward, Redbud Community Hospital, Box 6720, Clearlake, CA 95422; (707) 994-6486.

(Continued on Page 569)

(Continued from Page 568)

PHYSICIANS WANTED

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FT. CARSON, COLORADO. Staff physician needed for 125-bed, beautiful military hospital Emergency Room located at the foot of Pikes Peak. Excellent hunting, fishing, skiing, hiking, and other outdoor activities. An hour from Denver in a terrific community. BC/BE in a Primary Care specialty.

GRAND ISLAND, NEBRASKA. Staff physician needed for 139-bed hospital with moderate volume Emergency Room. Wonderful place to raise a family. Located two hours west of Lincoln. Superb medical staff and nursing group.

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CARLSBAD, NEW MEXICO. Full-time Emergency Department director and staff physician needed. This full-service community hospital has an annual Emergency Department volume of 10,000. Carlsbad, home of the Carlsbad Caverns, also boasts of abundant recreational activities. Enjoy water sports on the Pecos River or at the Lake Carlsbad Recreation Area.

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(Continued on Page 570)

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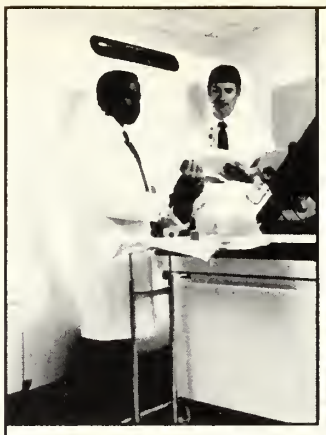

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CALIFORNIA, MONTEREY BAY. Full-/part-time positions available with Monterey Bay's largest and most successful Urgent Care network. Generous guarantee, incentive plan, and benefit package. Malpractice covered. Practice in California's most beautiful coastal recreational area. BC/BE Emergency Medicine or Family Practice specialists preferred. Contact Bob Morris, MD, FACEP, Doctors on Duty Medical Clinics, 223 Mt Hermon Rd, Scotts Valley, CA 95066; (408) 438-9341.

OREGON. General Internal Medicine, BC/BE, sought for 10 member, multispecialty group in beautiful rural community, population 16,500, 38 miles southwest of Portland. Send CV to Administrator, 420 E. Fifth St, McMinnville, OR 97128; (503) 472-6161.

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WANTED: CLINICIAN/TEACHER to join 15 General Internists at Santa Clara Valley Medical Center and Clinics, a public hospital affiliated with Stanford University. Applicants should be BE (BC if eligible more than two years), love clinical medicine and patient care, enjoy housestaff and medical students, and have excellent sense of humor to deal with usual politics of university-affiliated public hospital/clinic work. Send inquiries, CV to Kent Imai, MD, Chief, Primary Care Division, Department of Medicine, Santa Clara Valley Medical Center, 750 S Bascom Ave, San Jose, CA 95128.

TWO FACULTY POSITIONS—University of Nevada School of Medicine, Reno and Las Vegas Family Practice. Assistant/associate professor—assistant residency directors in clinical, non-tenure track, full-time faculty positions. Appointment DOE. Must be BE/BC and eligible for licensure in Nevada. Two young, successful programs with all resident positions filled. Responsibilities include teaching, administration, and patient care including Obstetrics. Search will continue until positions are filled. Send CV to George H. Hess, MD, Chairman, Department of Family and Community Medicine, University of Nevada School of Medicine, Reno, NV 89557. AA/EOE.

PULMONARY/CRITICAL CARE PHYSICIAN. BC/BE physician needed to replace retiring partner in large, well equipped, multispecialty clinic to begin late 1992. Practice is limited to Pulmonary or Critical Care medicine. Interest and ability in teaching at fellow level (University of Utah) is mandatory, and clinical research is encouraged. Salt Lake City is a beautiful Intermountain West city with a wonderful climate, community, and year-round outdoor recreation. Interested applicants send CV and names of three references to Jane Renwick, Medical Staff Secretary, Salt Lake Clinic, 333 S Ninth E, Salt Lake City, UT 84102; (801) 535-8319.

BC/BE GASTROENTEROLOGIST NEEDED. Busy office practice. 27 doctor multispecialty clinic. Mountain locale. Guaranteed salary. Excellent benefits. CV to Mike McCraley, Ogden Clinic, 4650 Harrison, Ogden, UT 84403; (800) 234-5637.

BC/BE GENERAL INTERNIST NEEDED. Nine physician department in 27 doctor multispecialty clinic. Guaranteed salary. Excellent benefits. CV to Mike McCraley, Ogden Clinic, 4650 Harrison, Ogden, UT 84403; (800) 234-5637.

INTERNIST/FAMILY PRACTITIONER. Join progressive and well respected community clinic in desirable San Francisco/Oakland bay area. Position available for Internist or Family Practitioner with strong Internal Medicine background. Limited call, 3.5-5 day work week; salary plus fee-for-service for inpatient care. Excellent fringe benefits which include malpractice insurance. Send CV to Pat Royball, Personnel, La Clinica de la Raza, 1515 Fruitvale, Oakland, CA 94601; (510) 534-0078.

NEONATOLOGIST to direct a Level II nursery in a community hospital just south of San Francisco. This individual will be responsible administratively for the organization of all neonatal services to the 2000 babies delivered yearly and will participate in the teaching program and the clinical service at the affiliated Level III nursery. Contact Toshiko Hirata, California Pacific Medical Center (formerly Children's Hospital of San Francisco), Newborn Services, 3850 California St, San Francisco, CA 94118; (415) 750-6052.

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BEAUTIFUL OREGON COAST. Private multispecialty cooperative with excellent facility seeking Family Practice physician to join five full-time Family Practitioners. Full spectrum of Family Practice. In-house lab, x-ray, day surgery. Contact Marce Knight, 1900 Woodland Dr, Coos Bay, OR 97420; (503) 267-5151, ext 294 or (800) 234-1231.

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(Continued on Page 571)

(Continued from Page 570)

PHYSICIANS WANTED

GENERAL SURGEON. Full-time BC/BE General Surgeon for multispecialty group in southeast Los Angeles. Office/hospital and consulting practice. Spanish a plus. Top salary, benefits, and malpractice insurance. Potential for shareholdership second year. Send CV to Craig Kaner, Administrator, All Care Medical Group, Inc., 2675 E. Slauson Ave, Huntington Park, CA 90255; (213) 589-6681.

OB/GYN. Full-time BC/BE OB/GYN for multispecialty group in southeast Los Angeles. Office/hospital practice. Spanish a plus. Top salary, benefits, and malpractice insurance. Potential for shareholdership second year. Send CV to Craig Kaner, Administrator, All Care Medical Group, Inc., 2675 E. Slauson Ave, Huntington Park, CA 90255; (213) 589-6681.

COASTAL CALIFORNIA. San Luis Obispo, Internal Medicine BC/BE, busy multispecialty group, eight miles to beach, excellent schools, recently rated "best small town in USA." Rewarding hospital-based practice. Guaranteed salary, malpractice covered, excellent call rotation. Call or send CV to Fran Wolke, San Luis Obispo General Hospital, PO Box 8113, San Luis Obispo, CA 93403-8113; (805) 549-4936.

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ONCOLOGIST WANTED. Oncologist wanted to join an Internal Medicine group in San Diego, California. Guarantee plus commission. Opportunity to join full partnership in two years. Number 250, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

(Continued on Page 572)

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(Continued from Page 571)

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INVASIVE CARDIOLOGIST. Beautiful Pacific northwest. Excellent opportunity. Quality care, heart institute setting. Please send current CV to Number 245, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

OB/GYN. BC/BE to join 20 physician (OB, Pediatrics, Internal Medicine) practice in sunny central Washington. Reasonable call schedule with three OB/GYN department. Loan repayment program available. Competitive salary, excellent benefit package including vacation at 30 days per year and professional liability. Contact Ann Garza, Yakima Valley Farm Workers Clinic, PO Box 190, Toppenish, WA 98948; (509) 865-5898.

BOULDER COLORADO—BC/BE FAMILY PRACTICE PHYSICIAN for busy clinic serving low income and underserved people. Position includes faculty appointment at the University of Colorado Department of Family Medicine and the opportunity to train residents. Clinic is eight miles from Boulder and 30 miles from Denver, Colorado. Send résumé to CCFHS, 1345 Plaza Ct N., Lafayette, CO 80026; or call Pete Leibig at (303) 665-9310 for more details.

VA OUTPATIENT CLINIC, POCATELLO, IDAHO, has current vacancy for staff physician (full-time) Monday through Friday, daytime clinic hours. For application or further information contact P. Herning, MD; (801) 582-1565, ext 1196 or K. Merrill, personnel; (801) 584-1284. VA Medical Center, 500 Foothill Dr, Salt Lake City, UT 84148. The VA is an equal opportunity employer.

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EUGENE, OREGON. INTERNIST, BC/BE, to join well established 44 physician Primary Care group. Excellent schools. Abundant cultural and recreational opportunities. Near Cascade Mountains and coast. Home of University of Oregon. Please send CV to David Strutin, MD, Oregon Medical Group, 495 Oakway Rd, Eugene, OR 97401; or call (503) 342-2134.

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OB/GYN—NORTHERN CALIFORNIA. Four person, single specialty group seeking recently trained US graduate. Send CV to Jack Rowland, 1400 Florida, Ste 205, Modesto, CA 95350.

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(Continued on Page 573)

(Continued from Page 572)

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(Continued on Page 574)

(Continued from Page 573)

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Third Annual Congenital Heart Disease in the Adult. January 19-21, 1992. San Diego, California. Fees: $435 for ACC members; $500 for nonmembers; $290 for residents, fellows-in-training, nurses, and technicians. 21 category 1 credit hours. For information, call **American College of Cardiology; (800) 253-4636, ext 695; FAX (301) 897-9745.**

JANUARY 22-25. THE SAN DIEGO CONFERENCE ON RESPONDING TO CHILD MALTREATMENT, Center for Child Protection, Children's Hospital. Hyatt Regency Hotel, La Jolla, California. Wednesday-Saturday, 28 hours, $345 before 11/30/91. Contact (619) 495-4940.

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Alaska State Medical Association—4107 Laurel St, Anchorage 99508. (907) 562-2662. Annual Meeting: 1992, date and location to be announced.

Arizona Medical Association, Inc—810 W Bethany Home Rd, Phoenix 85013. (602) 246-8901. Annual Meeting: June 4-6, 1992, Scottsdale.

California Medical Association—PO Box 7690, San Francisco 94120-7690. (415) 541-0900. Annual Meeting: March 13-18, 1992, Disneyland Hotel, Anaheim.

Colorado Medical Society—PO Box 17550, Denver 80217-0550. (303) 779-5455. Annual Meeting: 1992, date and location to be announced.

Hawaii Medical Association—1360 S Beretania, Honolulu 96814. (808) 536-7702. Annual Meeting: 1992, date and location to be announced.

Idaho Medical Association—305 W Jefferson, PO Box 2668, Boise 83701. (208) 344-7888. Annual Meeting: 1992, date and location to be announced.

Montana Medical Association—2012 11th Ave, Suite 12, Helena 59601. (406) 443-4000. Annual Meeting: 1992, date and location to be announced.

Nevada State Medical Association—3660 Baker Lane, Reno 89502. (702) 825-6788. Annual Meeting: April 23-26, 1992, Sheraton Grand Torrey Pines, La Jolla, California.

New Mexico Medical Society—7770 Jefferson, Suite 400, Albuquerque 87109. (505) 828-0237. Annual Meeting: May 14-16, 1992, Albuquerque.

Oregon Medical Association—5210 SW Corbett Ave, Portland 97201. (503) 226-1555. Annual Meeting (House of Delegates only): 1992, date and location to be announced.

Utah Medical Association—540 E Fifth South, Salt Lake City 84102. (801) 355-7477. September 16-19, 1992, University Park Hotel, Salt Lake City.

Washington State Medical Association—900 United Airlines Bldg, 2033 6th Ave, Seattle 98121. (206) 441-WSMA. Annual Meeting: September 9-12, 1992, Jantzen Beach, Oregon.

Wyoming Medical Society—PO Drawer 4009, Cheyenne 82003-4009. (307) 635-2424. Annual Meeting: June 11-13, 1992, Jackson Lake Lodge, Moran.

ADVERTISING INDEX

BLUE CROSS OF CALIFORNIA 447, 448, 449

BLUE SHIELD OF CALIFORNIA 469

CEDAR-SINAI MEDICAL CENTER 452

CIGNA HEALTHPLAN 569

CLASSIFIED ADVERTISING 564, 566, 567, 568, 569, 570, 571, 572, 573, 574

CNA INSURANCE 459

COSTAL GOVERNMENT SERVICES INC 568

ELI LILLY & COMPANY
Axid 462, 463

FHP HEALTH CARE 571

FOREST PHARMACEUTICALS INC.
AeraBid 454, 455, 456

GLAXO INC.
Zantac ..... 3rd and 4th covers

INSURANCE CORPORATION OF AMERICA 561

KAISER PERMANENTE 567

LAMPLIGHT SOFTWARE 456

MERCK SHARP & DOHME
Mevacar 477, 478, 479, 480

PALISADES PHARMACEUTICALS INC.
Yacon 472

PHYSICIANS INTERINDEMNITY INSURANCE 471

G.D. SEARLE & COMPANY
Calan SR 451

UNIHEALTH AMERICA 452

UNIVERSITY MICROFILM 452

UNIVERSITY SOUTHERN CALIFORNIA
University Hospital 467

UPJOHN COMPANY
Ragaine ..... 2nd cover, 445

US AIR FORCE 565

WELLS FARGO BANK 465

THE WESTERN JOURNAL OF MEDICINE
Medical Student Writing Award 460
Special Issues 562
Subscription 445, 474

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Zantac®

ranitidine HCl/Glaxo 150 mg and 300 mg tablets

Zantac® 150 Tablets
(ranitidine hydrochloride)

Zantac® 300 Tablets
(ranitidine hydrochloride)

Zantac® Syrup
(ranitidine hydrochloride)

BRIEF SUMMARY

The following is a brief summary only. Before prescribing, see complete prescribing information in Zantac® product labeling.

INDICATIONS AND USAGE: Zantac® is indicated in.
1. Short-term treatment of **active duodenal ulcer.** Most patients heal within four weeks.
2. **Maintenance therapy** for duodenal ulcer patients at reduced dosage after healing of acute ulcers.
3. The treatment of **pathological hypersecretory conditions** (eg, Zollinger-Ellison syndrome and systemic mastocytosis).
4. Short-term treatment of **active, benign gastric ulcer.** Most patients heal within six weeks and the usefulness of further treatment has not been demonstrated.
5. Treatment of **gastroesophageal reflux disease (GERD).** Symptomatic relief commonly occurs within one or two weeks after starting therapy. Therapy for longer than six weeks has not been studied.

In active duodenal ulcer; active, benign gastric ulcer; hypersecretory states; and GERD, concomitant antacids should be given as needed for relief of pain.

CONTRAINDICATIONS: Zantac® is contraindicated for patients known to have hypersensitivity to the drug.

PRECAUTIONS:

General: 1. Symptomatic response to Zantac® therapy does not preclude the presence of gastric malignancy.

2. Since Zantac is excreted primarily by the kidney, dosage should be adjusted in patients with impaired renal function (see DOSAGE AND ADMINISTRATION). Caution should be observed in patients with hepatic dysfunction since Zantac is metabolized in the liver.

Laboratory Tests: False-positive tests for urine protein with Multistix® may occur during Zantac therapy, and therefore testing with sulfosalicylic acid is recommended.

Drug Interactions: Although Zantac has been reported to bind weakly to cytochrome P-450 *in vitro*, recommended doses of the drug do not inhibit the action of the cytochrome P-450-linked oxygenase enzymes in the liver. However, there have been isolated reports of drug interactions that suggest that Zantac may affect the bioavailability of certain drugs by some mechanism as yet unidentified (eg, a pH-dependent effect on absorption or a change in volume of distribution).

Carcinogenesis, Mutagenesis, Impairment of Fertility: There was no indication of tumorigenic or carcinogenic effects in lifespan studies in mice and rats at doses up to 2,000 mg/kg/d.

Ranitidine was not mutagenic in standard bacterial tests (*Salmonella, Escherichia coli*) for mutagenicity at concentrations up to the maximum recommended for these assays.

In a dominant lethal assay, a single oral dose of 1,000 mg/kg to male rats was without effect on the outcome of two matings per week for the next nine weeks.

Pregnancy: ***Teratogenic Effects: Pregnancy Category B:*** Reproduction studies have been performed in rats and rabbits at doses up to 160 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to Zantac. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: Zantac is secreted in human milk. Caution should be exercised when Zantac is administered to a nursing mother.

Pediatric Use: Safety and effectiveness in children have not been established.

Use in Elderly Patients: Ulcer healing rates in elderly patients (65 to 82 years of age) were no different from those in younger age groups. The incidence rates for adverse events and laboratory abnormalities were also not different from those seen in other age groups.

ADVERSE REACTIONS: The following have been reported as events in clinical trials or in the routine management of patients treated with Zantac®. The relationship to Zantac therapy has been unclear in many cases. Headache, sometimes severe, seems to be related to Zantac administration.

Central Nervous System: Rarely, malaise, dizziness, somnolence, insomnia, and vertigo. Rare cases of reversible mental confusion, agitation, depression, and hallucinations have been reported, predominantly in severely ill elderly patients. Rare cases of reversible blurred vision suggestive of a change in accommodation have been reported.

Cardiovascular: As with other H_2-blockers, rare reports of arrhythmias such as tachycardia, bradycardia, atrioventricular block, and premature ventricular beats.

Gastrointestinal: Constipation, diarrhea, nausea/vomiting, abdominal discomfort/pain, and rare reports of pancreatitis.

Hepatic: In normal volunteers, SGPT values were increased to at least twice the pretreatment levels in 6 of 12 subjects receiving 100 mg qid intravenously for seven days, and in 4 of 24 subjects receiving 50 mg qid intravenously for five days. There have been occasional reports of hepatitis, hepatocellular or hepatocanalicular or mixed, with or without jaundice. In such circumstances, ranitidine should be immediately discontinued. These events are usually

Zantac® 150 and 300 (ranitidine hydrochloride) Tablets
Zantac® (ranitidine hydrochloride) Syrup

reversible, but in exceedingly rare circumstances death has occurred.

Musculoskeletal: Rare reports of arthralgias.

Hematologic: Blood count changes (leukopenia, granulocytopenia, thrombocytopenia) have occurred in a few patients. These were usually reversible. Rare cases of agranulocytosis, pancytopenia, sometimes with marrow hypoplasia, and aplastic anemia have been reported.

Endocrine: Controlled studies in animals and man have shown no stimulation of any pituitary hormone by Zantac and no antiandrogenic activity, and cimetidine-induced gynecomastia and impotence in hypersecretory patients have resolved when Zantac has been substituted. However, occasional cases of gynecomastia, impotence, and loss of libido have been reported in male patients receiving Zantac, but the incidence did not differ from that in the general population.

Integumentary: Rash, including rare cases suggestive of mild erythema multiforme, and, rarely, alopecia.

Other: Rare cases of hypersensitivity reactions (eg, bronchospasm, fever, rash, eosinophilia), anaphylaxis, angioneurotic edema, and small increases in serum creatinine.

OVERDOSAGE: Information concerning possible overdosage and its treatment appears in the full prescribing information.

DOSAGE AND ADMINISTRATION: (See complete prescribing information in Zantac® product labeling).

Active Duodenal Ulcer: The current recommended adult oral dosage is 150 mg or 10 ml (2 teaspoonfuls equivalent to 150 mg of ranitidine) twice daily. An alternate dosage of 300 mg or 20 ml (4 teaspoonfuls equivalent to 300 mg of ranitidine) once daily at bedtime can be used for patients in whom dosing convenience is important. The advantages of one treatment regimen compared to the other in a particular patient population have yet to be demonstrated.

Maintenance Therapy: The current recommended adult oral dosage is 150 mg or 10 ml (2 teaspoonfuls equivalent to 150 mg of ranitidine) at bedtime.

Pathological Hypersecretory Conditions (such as Zollinger-Ellison syndrome): The current recommended adult oral dosage is 150 mg or 10 ml (2 teaspoonfuls equivalent to 150 mg of ranitidine) twice a day. In some patients it may be necessary to administer Zantac® 150-mg doses more frequently. Doses should be adjusted to individual patient needs, and should continue as long as clinically indicated. Doses up to 6 g/d have been employed in patients with severe disease.

Benign Gastric Ulcer: The current recommended adult oral dosage is 150 mg or 10 ml (2 teaspoonfuls equivalent to 150 mg of ranitidine) twice a day.

GERD: The current recommended adult oral dosage is 150 mg or 10 ml (2 teaspoonfuls equivalent to 150 mg of ranitidine) twice a day.

Dosage Adjustment for Patients with Impaired Renal Function: On the basis of experience with a group of subjects with severely impaired renal function treated with Zantac, the recommended dosage in patients with a creatinine clearance less than 50 ml/min is 150 mg or 10 ml (2 teaspoonfuls equivalent to 150 mg of ranitidine) every 24 hours. Should the patient's condition require, the frequency of dosing may be increased to every 12 hours or even further with caution. Hemodialysis reduces the level of circulating ranitidine. Ideally, the dosage schedule should be adjusted so that the timing of a scheduled dose coincides with the end of hemodialysis.

HOW SUPPLIED: Zantac® 300 Tablets (ranitidine hydrochloride equivalent to 300 mg of ranitidine) are yellow, capsule-shaped tablets embossed with "ZANTAC 300" on one side and "Glaxo" on the other. They are available in bottles of 30 (NDC 0173-0393-40) tablets and unit dose packs of 100 (NDC 0173-0393-47) tablets.

Zantac® 150 Tablets (ranitidine hydrochloride equivalent to 150 mg of ranitidine) are white tablets embossed with "ZANTAC 150" on one side and "Glaxo" on the other. They are available in bottles of 60 (NDC 0173-0344-42) and 100 (NDC 0173-0344-09) tablets and unit dose packs of 100 (NDC 0173-0344-47) tablets.

Store between 15° and 30° C (59° and 86° F) in a dry place. Protect from light. Replace cap securely after each opening.

Zantac® Syrup, a clear, peppermint-flavored liquid, contains 16.8 mg of ranitidine hydrochloride equivalent to 15 mg of ranitidine per 1 ml in bottles of 16 fluid ounces (one pint) (NDC 0173-0383-54).

Store between 4° and 25° C (39° and 77° F). Dispense in tight, light-resistant containers as defined in the USP/NF.

July 1990

Glaxo Pharmaceuticals
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Research Triangle Park, NC 27709

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VOLUME 155 • NUMBER 6 DECEMBER 1991

BIOMEDICAL SCIENCE

605 Jejunal Brush-Border Folate Hydrolase—A Novel Enzyme
C H HALSTED

610 Intravenous Immune Globulin Use in Patients With Human Immunodeficiency Virus-Related Thrombocytopenia Who Require Dental Extraction
M U RARICK, P BURIAN, N DE GUZMAN, B ESPINA, T MONTGOMERY, D JAMIN, and A M LEVINE

ARTICLES

613 Screening for Hepatitis B During Pregnancy—Awareness of Current Recommendations Among Washington Hospitals
T R ENG, M L BORGES, V K HARLIN, and J M KOBAYASHI

616 Charges for Comprehensive Obstetric Care at Teaching and Nonteaching Hospitals—A Comparison
G S GORDON, S E SEFCIK, and J P LO GERFO

CONFERENCES AND REVIEWS

621 Hemobilia—Evaluation of Current Diagnosis and Treatment
S W MERRELL and P D SCHNEIDER

626 Status Epilepticus—Clinical Features, Pathophysiology, and Treatment
C WATSON

EPITOMES

632 Important Advances in Urology

ALERTS, NOTICES, AND CASE REPORTS

637 Fatal Salicylate Toxicity From Bismuth Subsalicylate
S J SAINSBURY

639 Ciguatera Fish Poisoning in San Francisco, California, Caused by Imported Barracuda
R J GELLER, K R OLSON, and P E SENÉCAL

642 Sarcoidosis of the Breast, Central Nervous System, and Exocrine Glands in a Patient With Sicca Symptoms
K H FYE and R H HUNTER

644 Isoniazid Overdose—Successful Treatment With Pyridoxine and Hemodialysis
J M CASH and E T ZAWADA, Jr

RADIOLOGIC CASE

647 A 2-Year-Old Girl With Seizures and Fever
A N KAROLEWSKI and V C POIRIER

MEDICINE AND SOCIETY

649 Participation of Colorado Pediatricians and Family Physicians in the Medicaid Program
S BERMAN, S WASSERMAN, and S GRIMM

653 Obstetric Care, Medicaid, and Family Physicians—How Policy Changes Affect Physicians' Attitudes
T S NESBITT, J L TANJI, J E SCHERGER, and N B KAHN

COMMENTARY

658 Teething as a Cause of Death—A Historical Review
H L GIBBONS and C K HEBDON

EDITORIALS

660 Why Should Every Physician Know About Hemobilia? • Dietary Folate—The Digestible Vitamin

CORRESPONDENCE

663 Taxes and Abortion • Positive Preemployment Urine Drug Screen Caused by Foreign-Manufactured Vitamin Formulation

LESSONS FROM THE PRACTICE

664 The Ill-fated Child
G ZUCCONI

666 My Own Awakening
R J REINER

OTHER FEATURES

598 Continuing Medical Education Activities in California, Hawaii, and Nevada; Colorado; Idaho; New Mexico; Utah; Washington

667 Consultants

670 Volume Index

681 Subscription Information

685 Instructions for Authors

686 Classified Advertising

700 Western State Medical Associations' Meetings

Poems: 615, 620, 662

Detailed Table of Contents: 582, 586, 588

Official Journal of the Alaska State Medical Association, the Arizona Medical Association, the California Medical Association, the Denver Medical Society, the Idaho Medical Association, the Nevada State Medical Association, the New Mexico Medical Society, the Utah Medical Association, the Washington State Medical Association, and the Wyoming Medical Society.

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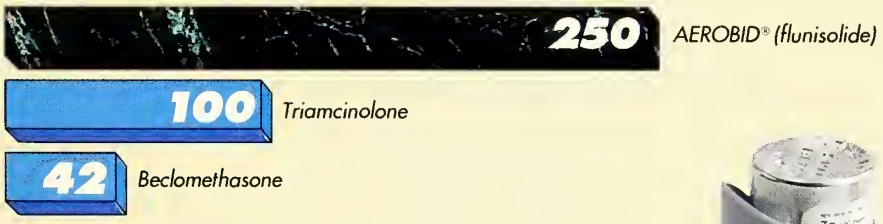

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CONTRAINDICATIONS

AeroBid Inhaler is contraindicated in the primary treatment of status asthmaticus or other acute episodes of asthma where intensive measures are required.

Hypersensitivity to any of the ingredients of this preparation contraindicates its use

WARNINGS

Particular care is needed in patients who are transferred from systemically active corticosteroids to AeroBid Inhaler because deaths due to adrenal insufficiency have occurred in asthmatic patients during and after transfer from systemic corticosteroids to aerosol corticosteroids. After withdrawal from systemic corticosteroids, a number of months are required for recovery of hypothalamic-pituitary-adrenal (HPA) function. During this period of HPA suppression, patients may exhibit signs and symptoms of adrenal insufficiency when exposed to trauma, surgery or infections, particularly gastroenteritis. Although AeroBid Inhaler may provide control of asthmatic symptoms during these episodes, it does NOT provide the systemic steroid that is necessary for coping with these emergencies

During periods of stress or a severe asthmatic attack, patients who have been withdrawn from systemic corticosteroids should be instructed to resume systemic steroids (in large doses) immediately and to contact their physician for further instruction. These patients should also be instructed to carry a warning card indicating that they may need supplementary systemic steroids during periods of stress or severe asthma attack. To assess the risk of adrenal insufficiency in emergency situations, routine tests of adrenal cortical function, including measurement of early morning resting cortisol levels, should be performed periodically in all patients. An early morning resting cortisol level may be accepted as normal if it falls at or near the normal mean level

Localized infections with Candida albicans or Aspergillus niger have occurred in the mouth and pharynx and occasionally in the larynx. Positive cultures for oral Candida may be present in up to 34% of patients. Although the frequency of clinically apparent infection is considerably lower, these infections may require treatment with appropriate antifungal therapy or discontinuance with AeroBid Inhaler

AeroBid Inhaler is not to be regarded as a bronchodilator and is not indicated for rapid relief of bronchospasm.

Patients should be instructed to contact their physician immediately when episodes of asthma that are not responsive to bronchodilators occur during the course of treatment. During such episodes, patients may require therapy with systemic corticosteroids.

There is no evidence that control of asthma can be achieved by administration of the drug in amounts greater than the recommended doses, which appear to be the therapeutic equivalent of approximately 10 mg/day of oral prednisone. Theoretically, the use of inhaled corticosteroids with alternate day prednisone systemic treatment should be accompanied by more HPA suppression than a therapeutically equivalent regimen of either alone.

Transfer of patients from systemic steroid therapy to AeroBid Inhaler may unmask allergic conditions previously suppressed by the systemic steroid therapy, e.g., rhinitis, conjunctivitis, and eczema

PRECAUTIONS

General: Because of the relatively high molar dose of flunisolide per activation in this preparation, and because of the evidence suggesting higher levels of systemic absorption with flunisolide than with other comparable inhaled corticosteroids, patients treated with AeroBid should be observed carefully for any evidence of systemic corticosteroid effect, including suppression of bone growth in children. Particular care should be taken in observing patients post-operatively or during periods of stress for evidence of a decrease in adrenal function. During withdrawal from oral steroids, some patients may experience symptoms of systemically active steroid withdrawal, e.g., joint and/or muscular pain, lassitude and depression, despite maintenance or even improvement of respiratory function.

In responsive patients, flunisolide may permit control of asthmatic symptoms without suppression of HPA function. Since flunisolide is absorbed into the circulation and can be systemically active, the beneficial effects of AeroBid Inhaler in minimizing or preventing HPA dysfunction may be expected only when recommended dosages are not exceeded.

The long-term effects of the drug in human subjects are still unknown. In particular, the local effects of the agent on developmental or immunologic processes in the mouth, pharynx, trachea, and lung are unknown. There is also no information about the possible long-term systemic effects of the agent.

The potential effects of the drug on acute, recurrent, or chronic pulmonary infections, including active or quiescent tuberculosis, are not known. Similarly, the potential effects of long-term administration of the drug on lung or other tissues are unknown.

Pulmonary infiltrates with eosinophilia may occur in patients on AeroBid Inhaler therapy. Although it is possible that in some patients this state may become manifest because of systemic steroid withdrawal when inhalational steroids are administered, a causative role for the drug and/or its vehicle cannot be ruled out.

Carcinogenesis: A 22-month study was conducted in Swiss derived mice to evaluate the carcinogenic potential of the drug. There was an increase in the incidence of pulmonary adenomas within the range of adenomas previously reported in the literature for untreated or control Swiss derived mice. An additional study is being conducted in a species with a lower incidence of spontaneous pulmonary tumors.

Impairment of fertility: Female rats receiving high doses of flunisolide (200 mcg/kg/day) showed some evidence of impaired fertility. Reproductive performance in the low (8 mcg/kg/day) and mid-dose (40 mcg/kg/day) groups was comparable to controls.

Pregnancy: Pregnancy Category C. As with other corticosteroids, flunisolide has been shown to be teratogenic in rabbits and rats at doses of 40 and 200 mcg/kg/day respectively. It was also fetotoxic in these animal reproductive studies. There are no adequate and well-controlled studies in pregnant women. Flunisolide should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because other corticosteroids are excreted in human milk, caution should be exercised when flunisolide is administered to nursing women.

ADVERSE REACTIONS

Adverse events reported in controlled clinical trials and long-term open studies in 514 patients treated with AeroBid are described below. Of those patients, 463 were treated for 3 months or longer, 407 for 6 months or longer, 287 for 1 year or longer, and 122 for 2 years or longer

Musculoskeletal reactions were reported in 35% of steroid-dependent patients in whom the dose of oral steroid was being tapered. This is a well-known effect of steroid withdrawal.

Incidence 10% or greater

Gastrointestinal: diarrhea (10%), nausea and/or vomiting (25%), upset stomach (10%); *General:* flu (10%); *Mouth and Throat:* sore throat (20%); *Nervous System:* headache (25%); *Respiratory:* cold symptoms (15%), nasal congestion (15%), upper respiratory infection (25%); *Special Senses:* unpleasant taste (10%).

Incidence 3-9%

Cardiovascular: palpitations, *Gastrointestinal:* abdominal pain, heartburn; *General:* chest pain, decreased appetite, edema, fever, *Mouth and Throat:* Candida infection; *Nervous System:* dizziness, irritability, nervousness, shakiness, *Reproductive:* menstrual disturbances, *Respiratory:* chest congestion, cough,* hoarseness, rhinitis, runny nose, sinus congestion, sinus drainage, sinus infection, sinusitis, sneezing, sputum, wheezing*, *Skin:* eczema, itching (pruritus), rash; *Special Senses:* ear infection, loss of smell or taste.

Incidence 1-3%

General: chills, increased appetite and weight gain, malaise, peripheral edema, sweating, weakness; *Cardiovascular:* hypertension, tachycardia; *Gastrointestinal:* constipation, dyspepsia, gas, *Hemic/Lymph:* capillary fragility, enlarged lymph nodes, *Mouth and Throat:* dry throat, glossitis, mouth irritation, pharyngitis, phlegm, throat irritation; *Nervous System:* anxiety, depression, faintness, fatigue, hyperactivity, hypoactivity, insomnia, moodiness, numbness, vertigo, *Respiratory:* bronchitis, chest tightness,* dyspnea, epistaxis, head stuffiness, laryngitis, nasal irritation, pleurisy, pneumonia, sinus discomfort, *Skin:* acne, hives, or urticaria, *Special Senses:* blurred vision, earache, eye discomfort, eye infection.

Incidences less than 1%, judged by investigators as possibly or probably drug-related: abdominal fullness, shortness of breath

*The incidences as shown of cough, wheezing, and chest tightness were judged by investigators to be possibly or probably drug-related. In placebo-controlled trials, the overall incidences of these adverse events (regardless of investigators' judgement of drug relationship) were similar for drug and placebo-treated groups. They may be related to the vehicle or delivery system.

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1. *National Heart, Lung, and Blood Institute National Asthma Education Program Expert Panel Report – Guidelines for the Diagnosis and Management of Asthma* Bethesda, Md US Dept of Health and Human Services, 1991
2. *Physicians' Desk Reference®* 45th ed Oradell, NJ Medical Economics Co Inc, 1991:955, 1862, 2026

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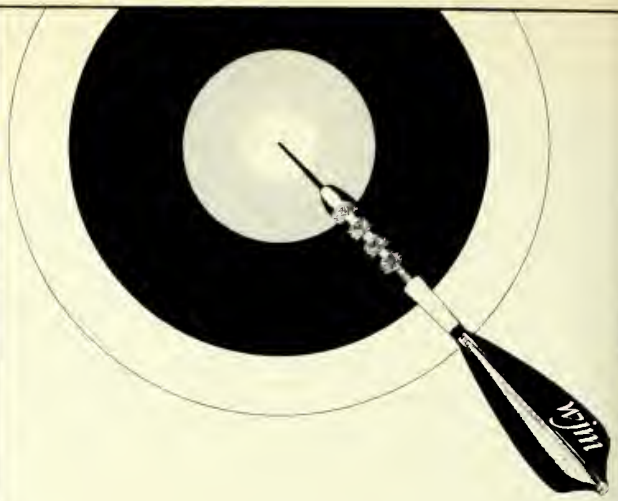

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VOLUME 155 • NUMBER 6 • DECEMBER 1991

CONTENTS

BIOMEDICAL SCIENCE

605 **Jejunal Brush-Border Folate Hydrolase—A Novel Enzyme**

CHARLES H. HALSTED, MD

From the Division of Clinical Nutrition and Metabolism, Department of Internal Medicine, University of California, Davis, School of Medicine.

610 **Intravenous Immune Globulin Use in Patients With Human Immunodeficiency Virus-Related Thrombocytopenia Who Require Dental Extraction**

MARK U. RARICK, MD; PAM BURIAN, PA-C; NELSON DE GUZMAN, PA-C; BYRON ESPINA; TERRI MONTGOMERY, RN; DENISE JAMIN, PharmD; and ALEXANDRA M. LEVINE, MD

From the Departments of Internal Medicine and Pharmacology, Section of Hematology, University of Southern California School of Medicine, Los Angeles.

ARTICLES

613 **Screening for Hepatitis B During Pregnancy—Awareness of Current Recommendations Among Washington Hospitals**

THOMAS R. ENG, VMD, MPH; MARY L. BORGES; VIVIAN K. HARLIN, MD, MSPH; and JOHN M. KOBAYASHI, MD, MPH

From the Division of Field Services, Epidemiology Program Office, Centers for Disease Control, US Public Health Service, Atlanta, Georgia; the Immunization Program, Washington State Department of Health, Olympia; and the Communicable Disease Epidemiology Office, Washington State Department of Health, Seattle. Dr Eng is now with the Office of Medical Services, US Peace Corps, Washington, DC.

616 **Charges for Comprehensive Obstetric Care at Teaching and Nonteaching Hospitals—A Comparison**

GILAD S. GORDON, MD, MBA; STEPHAN E. SEFCIK, CPA, PhD; and JAMES P. LO GERFO, MD, MPH

From the Department of Medicine, School of Medicine, and the School of Business Administration, University of Washington, Seattle.

CONFERENCES AND REVIEWS

621 **Hemobilia—Evaluation of Current Diagnosis and Treatment**

STEVEN W. MERRELL, MD, and PHILIP D. SCHNEIDER, MD, PhD

From the Department of Surgery, University of Utah School of Medicine, Salt Lake City, and the Department of Surgery, University of California, Davis, School of Medicine, Sacramento. Dr Merrell is now with the Section of Vascular Surgery, Mayo Clinic, Rochester, Minnesota.

626 **Status Epilepticus—Clinical Features, Pathophysiology, and Treatment**

CRAIG WATSON, MD, PhD

From the Department of Neurology, University of California, Davis, School of Medicine, and the Sutter Neuroscience Center Epilepsy Program and Sacramento Comprehensive Epilepsy Program, Sacramento, California.

EPITOMES—IMPORTANT ADVANCES IN CLINICAL MEDICINE

Urology

Items of progress in urology. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance.

632 **Prostate-Specific Antigen**

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(Continued on Page 586)

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BuSpar® 10mg

(buspirone HCl)

Progressive Relief of Persistent Anxiety.

Please see references and brief summary on adjacent page.

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BuSpar® (buspirone HCl)

References: 1. Feighner JP, Cohn JB Analysis of individual symptoms in generalized anxiety—a pooled, multistudy, double-blind evaluation of buspirone *Neuropsychobiology* 1989,21 124-130 **2.** Newton RE, Marunycz JD, Alderdice MT, Napichello MJ Review of the side-effect profile of buspirone *Am J Med* 1986,80 (suppl 3B) 17-21 **3.** Lader M Assessing the potential for buspirone dependence or abuse and effects of its withdrawal *Am J Med* 1987,82 (suppl 5A) 20-26

Contraindications: Hypersensitivity to buspirone hydrochloride

Warnings: The administration of BuSpar to a patient taking a monoamine oxidase inhibitor (MAOI) may pose a hazard. Since blood pressure has become elevated when BuSpar was administered concomitantly with an MAOI, such concomitant use is not recommended BuSpar should not be employed in lieu of appropriate antipsychotic treatment

Precautions: ***General***—*Interference with cognitive and motor performance* Although buspirone is less sedating than other anxiolytics and does not produce significant functional impairment, its CNS effects in a given patient may not be predictable, therefore, patients should be cautioned about operating an automobile or using complex machinery until they are reasonably certain that buspirone does not affect them adversely Although buspirone has not been shown to increase alcohol-induced impairment in motor and mental performance, it is prudent to avoid concomitant use with alcohol

Potential for withdrawal reactions in sedative/hypnotic/anxiolytic drug dependent patients Because buspirone will not block the withdrawal syndrome often seen with cessation of therapy with benzodiazepines and other common sedative/hypnotic drugs, before starting buspirone withdraw patients gradually from their prior treatment, especially those who used a CNS depressant chronically Rebound or withdrawal symptoms may occur over varying time periods, depending in part on the type of drug and its elimination half-life The withdrawal syndrome can appear as any combination of irritability, anxiety, agitation, insomnia, tremor, abdominal cramps, muscle cramps, vomiting, sweating, flu-like symptoms without fever, and occasionally, even as seizures

Possible concerns related to buspirone's binding to dopamine receptors Because buspirone can bind to central dopamine receptors, a question has been raised about its potential to cause acute and chronic changes in dopamine mediated neurological function (eg, dystonia, pseudoparkinsonism, akathisia, and tardive dyskinesia) Clinical experience in controlled trials has failed to identify any significant neuroleptic-like activity, however, a syndrome of restlessness, appearing shortly after initiation of treatment, has been reported, the syndrome may be due to increased central noradrenergic activity or may be attributable to dopaminergic effects (ie, represent akathisia)

Information for Patients—Patients should be instructed to inform their physician about any medications, prescription or nonprescription, alcohol or drugs they are now taking or plan to take during treatment with buspirone, to inform their physician if they are pregnant, are planning to become pregnant, or become pregnant while taking buspirone, to inform their physician if they are breast feeding, and not to drive a car or operate potentially dangerous machinery until they experience how this medication affects them

Drug Interactions—Concomitant use with other CNS active drugs should be approached with caution (see **Warnings**) Concomitant use with trazodone may have caused 3- to 6-fold elevations on SGPT (ALT) in a few patients Concomitant administration of BuSpar and haloperidol resulted in increased serum haloperidol concentrations in normal volunteers The clinical significance is not clear Buspirone does not displace highly bound drugs like phenytoin, propranolol, and warfarin from serum proteins, but may displace less firmly bound drugs like digoxin However, there was one report of prolonged prothrombin time when buspirone was given to a patient also treated with warfarin, phenytoin, phenobarbital, digoxin, and Synthroid

Carcinogenesis, Mutagenesis, Impairment of Fertility—No evidence of carcinogenic potential was observed in rats or mice, buspirone did not induce point mutations, nor was DNA damage observed, chromosomal aberrations or abnormalities did not occur

Pregnancy: Teratogenic Effects—Pregnancy Category B Should be used during pregnancy only if clearly needed

Nursing Mothers—Administration to nursing women should be avoided if clinically possible

Pediatric Use—The safety and effectiveness have not been determined in individuals below 18 years of age

Use in the Elderly—No unusual, adverse, age-related phenomena have been identified in elderly patients receiving a total, modal daily dose of 15 mg

Use in Patients with Impaired Hepatic or Renal Function—Since buspirone is metabolized by the liver and excreted by the kidneys, it is not recommended in severe hepatic or renal impairment

Adverse Reactions (See also Precautions): ***Commonly Observed***—The more commonly observed untoward events, not seen at an equivalent incidence in placebo-treated patients, include dizziness, nausea, headache, nervousness, lightheadedness, and excitement

Associated with Discontinuation of Treatment—The more common events causing discontinuation included central nervous system disturbances (3 4%), primarily dizziness, insomnia, nervousness, drowsiness, lightheaded feeling, gastrointestinal disturbances (1 2%), primarily nausea, miscellaneous disturbances (1 1%), primarily headache and fatigue In addition, 3 4% of patients had multiple complaints, none of which could be characterized as primary

Incidence in Controlled Clinical Trials—Adverse events reported by 1% or more of 477 patients who received buspirone in four-week, controlled trials *Cardiovascular* Tachycardia/palpitations 1% *CNS* Dizziness 12%, drowsiness 10%, nervousness 5%, insomnia 3%, lightheadedness 3%, decreased concentration 2%, excitement 2%, anger/hostility 2%, confusion 2%, depression 2% *EENT* Blurred vision 2% *Gastrointestinal* Nausea 8%, dry mouth 3%, abdominal/gastric distress 2%, diarrhea 2%, constipation 1%, vomiting 1% *Musculoskeletal* Musculoskeletal aches/pains 1% *Neurological* Numbness 2%, paresthesia 1%, incoordination 1%, tremor 1% *Skin* Skin rash 1% *Miscellaneous* Headache 6%, fatigue 4%, weakness 2%, sweating/clamminess 1%

Other Events Observed During the Entire Premarketing Evaluation—The relative frequency of all other undesirable events reasonably associated with the use of buspirone in approximately 3000 subjects who took multiple doses of the drug under well-controlled, open, and uncontrolled conditions is defined as follows Frequent are those occurring in at least 1/100 patients, infrequent are those occurring in 1/100 to 1/1000 patients, and rare are those occurring in less than 1/1000 patients *Cardiovascular*—frequent nonspecific chest pain, infrequent syncope, hypotension, hypertension, rare cerebrovascular accident, congestive heart failure, myocardial infarction, cardiomyopathy, bradycardia *Central Nervous System*—frequent dream disturbances, infrequent depersonalization, dysphoria, noise intolerance, euphoria, akathisia, tearfulness, loss of interest, dissociative reaction, hallucinations, suicidal ideation, seizures, rare feelings of claustrophobia, cold intolerance, stupor, slurred speech, psychosis *EENT*—frequent tinnitus, sore throat, nasal congestion, infrequent redness and itching of the eyes, altered taste, altered smell, conjunctivitis, rare inner ear abnormality, eye pain, photophobia, pressure on eyes *Endocrine*—rare galactorrhea, thyroid abnormality *Gastrointestinal*—infrequent flatulence, anorexia, increased appetite, salivation, irritable colon, rectal bleeding, rare burning of the tongue *Genitourinary*—infrequent urinary frequency, urinary hesitancy, menstrual irregularity and spotting, dysuria, rare amenorrhea, pelvic inflammatory disease, enuresis, nocturia *Musculoskeletal*—infrequent muscle cramps, muscle spasms, rigid/stiff muscles, arthralgias *Neurological*—infrequent involuntary movements, slowed reaction time, rare muscle weakness *Respiratory*—infrequent hyperventilation, shortness of breath, chest congestion, rare epistaxis *Sexual Function*—infrequent decreased or increased libido, rare delayed ejaculation, impotence *Skin*—infrequent edema, pruritus, flushing, easy bruising, hair loss, dry skin, facial edema, blisters, rare acne, thinning of nails *Clinical Laboratory*—infrequent increases in hepatic aminotransferases (SGOT, SGPT), rare eosinophilia, leukopenia, thrombocytopenia *Miscellaneous*—infrequent weight gain, fever, roaring sensation in the head, weight loss, malaise, rare alcohol abuse, bleeding disturbance, loss of voice, hiccoughs

Postintroduction Clinical Experience—Rare occurrences of allergic reactions, cogwheel rigidity, dystonic reactions, ecchymosis, emotional lability, tunnel vision, and urinary retention have been reported Because of the uncontrolled nature of these spontaneous reports, a causal relationship to BuSpar has not been determined

Drug Abuse and Dependence: ***Controlled Substance Class***—Not a controlled substance

Physical and Psychological Dependence—Buspirone has shown no potential for abuse or diversion and there is no evidence that it causes tolerance, or either physical or psychological dependence However, since it is difficult to predict from experiments the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of buspirone misuse or abuse (eg, development of tolerance, incrementation of dose, drug-seeking behavior)

Overdosage: ***Signs and Symptoms***—At doses approaching 375 mg/day the following symptoms were observed nausea, vomiting, dizziness, drowsiness, miosis, and gastric distress No deaths have been reported in humans either with deliberate or accidental overdosage

Recommended Overdose Treatment—General symptomatic and supportive measures should be used along with immediate gastric lavage No specific antidote is known and dialyzability of buspirone has not been determined

For complete details, see Prescribing Information or consult your Mead Johnson Pharmaceuticals Representative

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ABSTRACTS DECEMBER 1991

(Eng TR, Borges ML, Harlin VK, Kobayashi JM: Screening for hepatitis B during pregnancy—Awareness of current recommendations among Washington hospitals. West J Med 1991 Dec; 155:613-615)

Acute care hospitals in Washington State that reported births (n = 77) were surveyed regarding their awareness of and compliance with the Centers for Disease Control recommendations for hepatitis B screening of pregnant women. Of these, 62 hospitals (81%) were aware of the recommendations and 39 (51%) routinely screened pregnant women who did not have a history of prenatal care at the time of delivery. In all, 68 hospitals (88%) had hepatitis B vaccine and 54 (70%) had hepatitis B immune globulin available on site. Despite awareness of the current recommendations for hepatitis B screening, barriers exist that prevent many hospitals from fully implementing them.

HEPATITIS B
HEPATITIS IN PREGNANCY
HEPATITIS SCREENING
HBsAg SCREENING
HEPATITIS B VACCINE
HEPATITIS B IMMUNE GLOBULIN

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(Continued from Page 582)

633 **BCG Vaccine in Urinary Bladder Cancer**
STANLEY A. BROSMAN, MD

633 **Medical Treatment of Benign Prostatic Hyperplasia**
JOSEPH D. SCHMIDT, MD

634 **Screening for Prostate Cancer**
MICHAEL T. MAC FARLANE, MD

634 **Laparoscopy in Urology**
GEORGE DANIELS, Jr, MD

635 **Extracorporeal Shock-Wave Lithotripsy With Minimal or No Anesthesia**
JOHN N. KABALIN, MD

635 **Male Infertility Update**
PHILIP WISE, MD

ALERTS, NOTICES, AND CASE REPORTS

637 **Fatal Salicylate Toxicity From Bismuth Subsalicylate**
STEVEN J. SAINSBURY, MD

From the Emergency Department, Twin Cities Community Hospital, Templeton, California.

639 **Ciguatera Fish Poisoning in San Francisco, California, Caused by Imported Barracuda**
RICHARD J. GELLER, MD; KENT R. OLSON, MD; and PIERRE E. SENÉCAL, MD

From the San Francisco Bay Area Regional Poison Control Center, San Francisco General Hospital Medical Center, the Fresno Regional Poison Control Center, Fresno Community Hospital and Medical Center, and University of California, San Francisco, School of Medicine.

642 **Sarcoidosis of the Breast, Central Nervous System, and Exocrine Glands in a Patient With Sicca Symptoms**
KENNETH H. FYE, MD, and RIPLEY H. HUNTER, MD

From the Division of Rheumatology, Department of Medicine, University of California, San Francisco, School of Medicine.

644 **Isoniazid Overdose—Successful Treatment With Pyridoxine and Hemodialysis**
JOSEPH M. CASH, MD, and EDWARD T. ZAWADA, Jr, MD

From the Department of Internal Medicine, University of South Dakota School of Medicine, Rapid City and Sioux Falls.

RADIOLOGIC CASE

647 **A 2-Year-Old Girl With Seizures and Fever**
ALICE N. KAROLEWSKI, MD, and VIRGINIA C. POIRIER, MD

From the Department of Radiology, University of California, Davis, Medical Center, Sacramento.

MEDICINE AND SOCIETY

649 **Participation of Colorado Pediatricians and Family Physicians in the Medicaid Program**
STEPHEN BERMAN, MD; STEPHANIE WASSERMAN, MSPH; and SUSAN GRIMM, MSPH

From the Department of Pediatrics, University of Colorado School of Medicine, Denver.

653 **Obstetric Care, Medicaid, and Family Physicians—How Policy Changes Affect Physicians' Attitudes**
THOMAS S. NESBITT, MD, MPH, JEFFREY L. TANJI, MD; JOSEPH E. SCHERGER, MD, MPH; and NORMAN B. KAHN, MD

From the University of California, Davis, School of Medicine.

(Continued on Page 588)

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Wnings: Verapamil should be avoided in patients with severe LV dysfunction (eg, ejection rion < 30%) or moderate to severe symptoms of cardiac failure and in patients with any dee of ventricular dysfunction if they are receiving a beta-blocker. Control milder heart failure w optimum digitalization and/or diuretics before Calan SR is used. Verapamil may occasionally oruce hypotension. Elevations of liver enzymes have been reported. Several cases have been deonstrated to be produced by verapamil. Periodic monitoring of liver function in patients on vepamil is prudent. Some patients with paroxysmal and/or chronic atrial flutter/fibrillation and accessory AV pathway (eg, WPW or LGL syndromes) have developed an increased antegrade conduction across the accessory pathway bypassing the AV node, producing a very rapid ventricular response or ventricular fibrillation after receiving I.V. verapamil (or digitalis). Because of is risk, oral verapamil is contraindicated in such patients. AV block may occur (2nd- and 3rdegree, 0.8%). Development of marked 1st-degree block or progression to 2nd- or 3rddegree block requires reduction in dosage or, rarely, discontinuation and institution of appropriate hpy. Sinus bradycardia, 2nd-degree AV block, sinus arrest, pulmonary edema and/or severe hytension were seen in some critically ill patients with hypertrophic cardiomyopathy who were rted with verapamil.

Pcautions: Verapamil should be given cautiously to patients with impaired hepatic function inevere dysfunction use about 30% of the normal dose) or impaired renal function, and patients shld be monitored for abnormal prolongation of the PR interval or other signs of overdosage. Vepamil may decrease neuromuscular transmission in patients with Duchenne's muscular dyophy and may prolong recovery from the neuromuscular blocking agent vecuronium. It may pecessary to decrease verapamil dosage in patients with attenuated neuromuscular transmission. Combined therapy with beta-adrenergic blockers and verapamil may result in additive netive effects on heart rate, atrioventricular conduction and/or cardiac contractility; there have pe reports of excessive bradycardia and AV block, including complete heart block. The risks of uch combined therapy may outweigh the benefits. The combination should be used only wi caution and close monitoring. Decreased metoprolol and propranolol clearance may occur wh either drug is administered concomitantly with verapamil. A variable effect has been seen wi combined use of atenolol. Chronic verapamil treatment can increase serum digoxin levels by0% to 75% during the first week of therapy, which can result in digitalis toxicity. In patients wi hepatic cirrhosis, verapamil may reduce total body clearance and extrarenal clearance of digoxin. The digoxin dose should be reduced when verapamil is given, and the patient carefully mtored. Verapamil will usually have an additive effect in patients receiving blood-pressure-oring agents. Disopyramide should not be given within 48 hours before or 24 hours after vepamil administration. Concomitant use of flecainide and verapamil may have additive effects on yocardial contractility, AV conduction, and repolarization. Combined verapamil and quinidine hpy in patients with hypertrophic cardiomyopathy should be avoided, since significant hytension may result. Concomitant use of lithium and verapamil may result in a lowering of sen lithium levels or increased sensitivity to lithium. Patients receiving both drugs must be mtored carefully. Verapamil may increase carbamazepine concentrations during combined use. Ritpin may reduce verapamil bioavailability. Phenobarbital may increase verapamil clearance. Vepamil may increase serum levels of cyclosporin. Verapamil may inhibit the clearance and nease the plasma levels of theophylline. Concomitant use of inhalation anesthetics and calcium angonists needs careful titration to avoid excessive cardiovascular depression. Verapamil may potiate the activity of neuromuscular blocking agents (curare-like and depolarizing); dosage ection may be required. Adequate animal carcinogenicity studies have not been performed. Or study in rats did not suggest a tumorigenic potential, and verapamil was not mutagenic in th Ames test. Pregnancy Category C. There are no adequate and well-controlled studies in orhant women. This drug should be used during pregnancy, labor, and delivery only if clearly nee ed. Verapamil is excreted in breast milk; therefore, nursing should be discontinued during vepamil use.

Aerse Reactions: Constipation (7.3%), dizziness (3.3%), nausea (2.7%), hypotension (2.5%), neache (2.2%), edema (1.9%), CHF, pulmonary edema (1.8%), fatigue (1.7%), dyspnea (1.4%), orycardia: HR < 50/min (1.4%), AV block: total 1°,2°,3° (1.2%), 2° and 3° (0.8%), rash (1 6), flushing (0.6%), elevated liver enzymes, reversible non-obstructive paralytic ileus. The fo wing reactions, reported in 1.0% or less of patients, occurred under conditions where a cal al relationship is uncertain: angina pectoris, atrioventricular dissociation, chest pain, claudicain, myocardial infarction, palpitations, purpura (vasculitis), syncope, diarrhea, dry mouth, ga ointestinal distress, gingival hyperplasia, ecchymosis or bruising, cerebrovascular accident, cc usion, equilibrium disorders, insomnia, muscle cramps, paresthesia, psychotic symptoms, shiness, somnolence, arthralgia and rash, exanthema, hair loss, hyperkeratosis, macules, sviting, urticaria, Stevens-Johnson syndrome, erythema multiforme, blurred vision, gynecoma, galactorrhea/hyperprolactinemia, increased urination, spotty menstruation, impotence.

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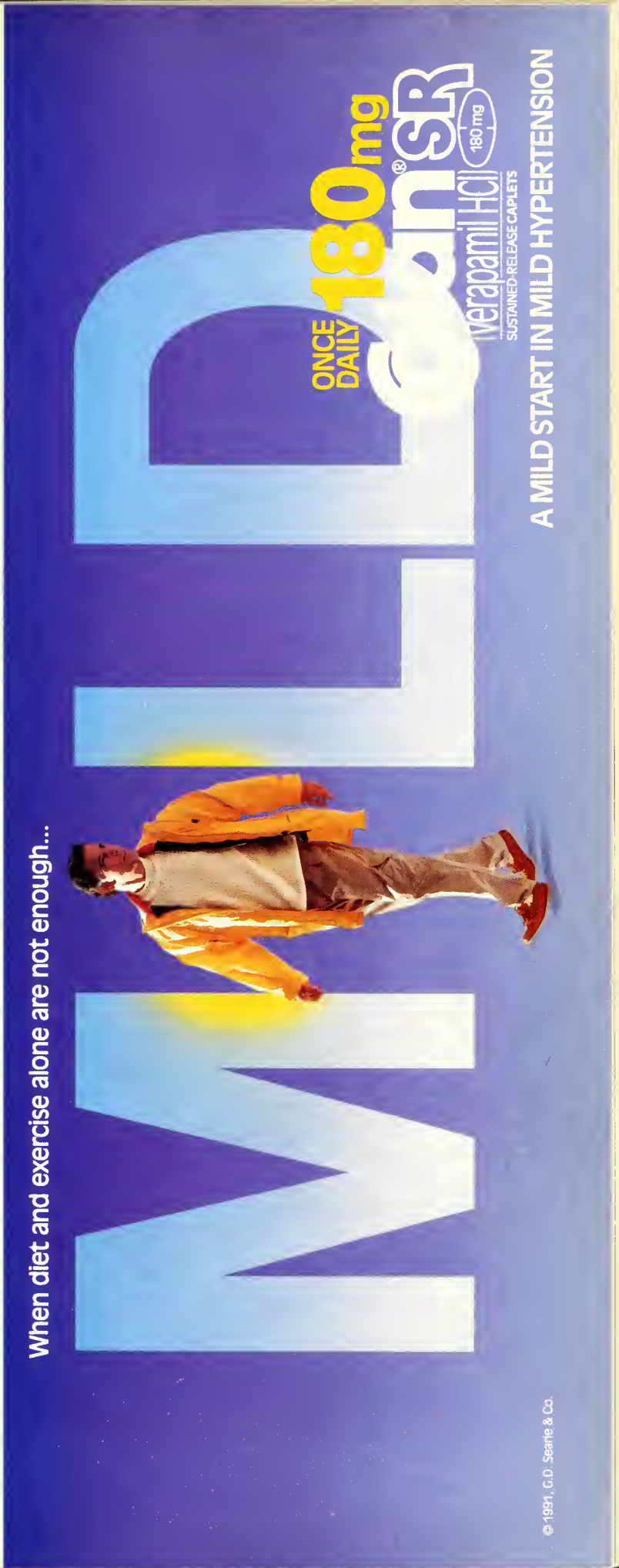

(Continued from Page 586)

COMMENTARY

658 **Teething as a Cause of Death—A Historical Review**
HARRY L. GIBBONS, MD, MPH, and C. KENT HEBDON, MD, MS
From the Salt Lake City-County Health Department and the University of Utah College of Medicine, Salt Lake City.

EDITORIALS

660 **Why Should Every Physician Know About Hemobilia?**
PHILIP SANDBLOM, MD
Dr Sandblom is Past President, University of Lund, Sweden, and Professor Emeritus of Surgery, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland.

660 **Dietary Folate—The Digestible Vitamin**
GARY M. GRAY, MD
Dr Gray is Professor of Medicine and Director, Digestive Disease Center, Stanford University School of Medicine, Stanford, California.

CORRESPONDENCE

663 **Taxes and Abortion**
LAURA HAMMONS, MD

663 **Positive Preemployment Urine Drug Screen Caused by Foreign-Manufactured Vitamin Formulation**
M. JOSEPH FEDORUK, MD, and LORETTA LEE, MD, MPH

LESSONS FROM THE PRACTICE

664 **The Ill-fated Child**
GEORGE ZUCCONI, MD
Dr Zucconi is in private practice in obstetrics and gynecology, La Mesa, California.

666 **My Own Awakening**
ROBERT J. REINER, MD
Dr Reiner is in private practice in urology in Lompoc, California.

OTHER FEATURES

598 **Continuing Medical Education Activities in California, Hawaii, and Nevada; Colorado; Idaho; New Mexico; Utah; Washington**
667 **Consultants**
670 **Volume Index**
681 **Subscription Information**
685 **Instructions for Authors**
686 **Classified Advertising**
700 **Western State Medical Associations' Meetings**
Poems: 615, 620, 662

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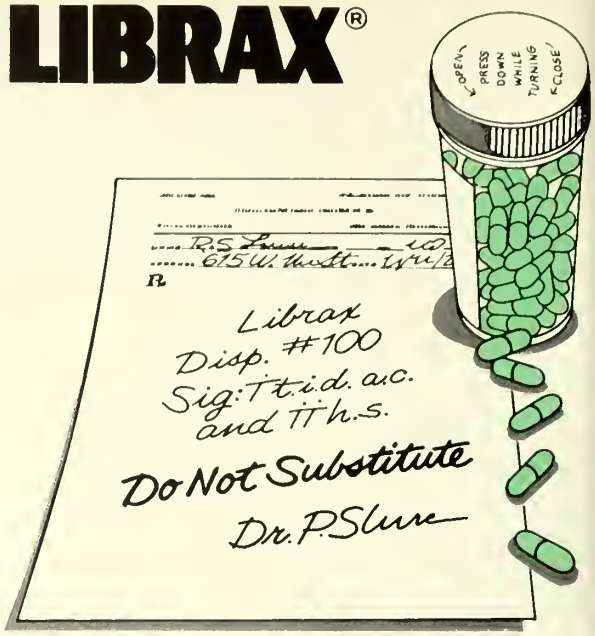

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Final classification of the less-than-effective indications requires further investigation.

Contraindications: Glaucoma; prostatic hypertrophy, benign bladder neck obstruction; hypersensitivity to chlordiazepoxide HCl and/or clidinium Br.
Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants, and against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving).

Usage in Pregnancy: **Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy. Advise patients to discuss therapy if they intend to or do become pregnant.**

As with all anticholinergics, inhibition of lactation may occur.
Withdrawal symptoms of the barbiturate type have occurred after discontinuation of benzodiazepines (see Drug Abuse and Dependence).
Precautions: In elderly and debilitated, limit dosage to smallest effective amount to preclude ataxia, oversedation, confusion (no more than 2 capsules/day initially; increase gradually as needed and tolerated). Though generally not recommended, if combination therapy with other psychotropics seems indicated, carefully consider pharmacology of agents, particularly potentiating drugs such as MAO inhibitors, phenothiazines. Observe usual precautions in presence of impaired renal or hepatic function. Paradoxical reactions reported in psychiatric patients. Employ usual precautions in treating anxiety states with evidence of impending depression; suicidal tendencies may be present and protective measures necessary. Variable effects on blood coagulation reported very rarely in patients receiving the drug and oral anticoagulants; causal relationship not established. Inform patients to consult physician before increasing dose or abruptly discontinuing this drug.
Adverse Reactions: No side effects or manifestations not seen with either compound alone reported with Librax. When chlordiazepoxide HCl is used alone, drowsiness, ataxia, confusion may occur, especially in elderly and debilitated; avoidable in most cases by proper dosage adjustment, but also occasionally observed at lower dosage ranges. Syncope reported in a few instances. Also encountered isolated instances of skin eruptions, edema, minor menstrual irregularities, nausea and constipation, extrapyramidal symptoms, increased and decreased libido—all infrequent, generally controlled with dosage reduction; changes in EEG patterns may appear during and after treatment; blood dyscrasias (including agranulocytosis), jaundice, hepatic dysfunction reported occasionally with chlordiazepoxide HCl, making periodic blood counts and liver function tests advisable during protracted therapy. Adverse effects reported with Librax typical of anticholinergic agents, *i.e.*, dryness of mouth, blurring of vision, urinary hesitancy, constipation. Constipation has occurred most often when Librax therapy is combined with other spasmolytics and/or low residue diets.
Drug Abuse and Dependence: Withdrawal symptoms similar to those noted with barbiturates and alcohol have occurred following abrupt discontinuance of chlordiazepoxide; more severe seen after excessive doses over extended periods; milder after taking continuously at therapeutic levels for several months. After extended therapy, avoid abrupt discontinuation and taper dosage. Carefully supervise addiction-prone individuals because of predisposition to habituation and dependence.

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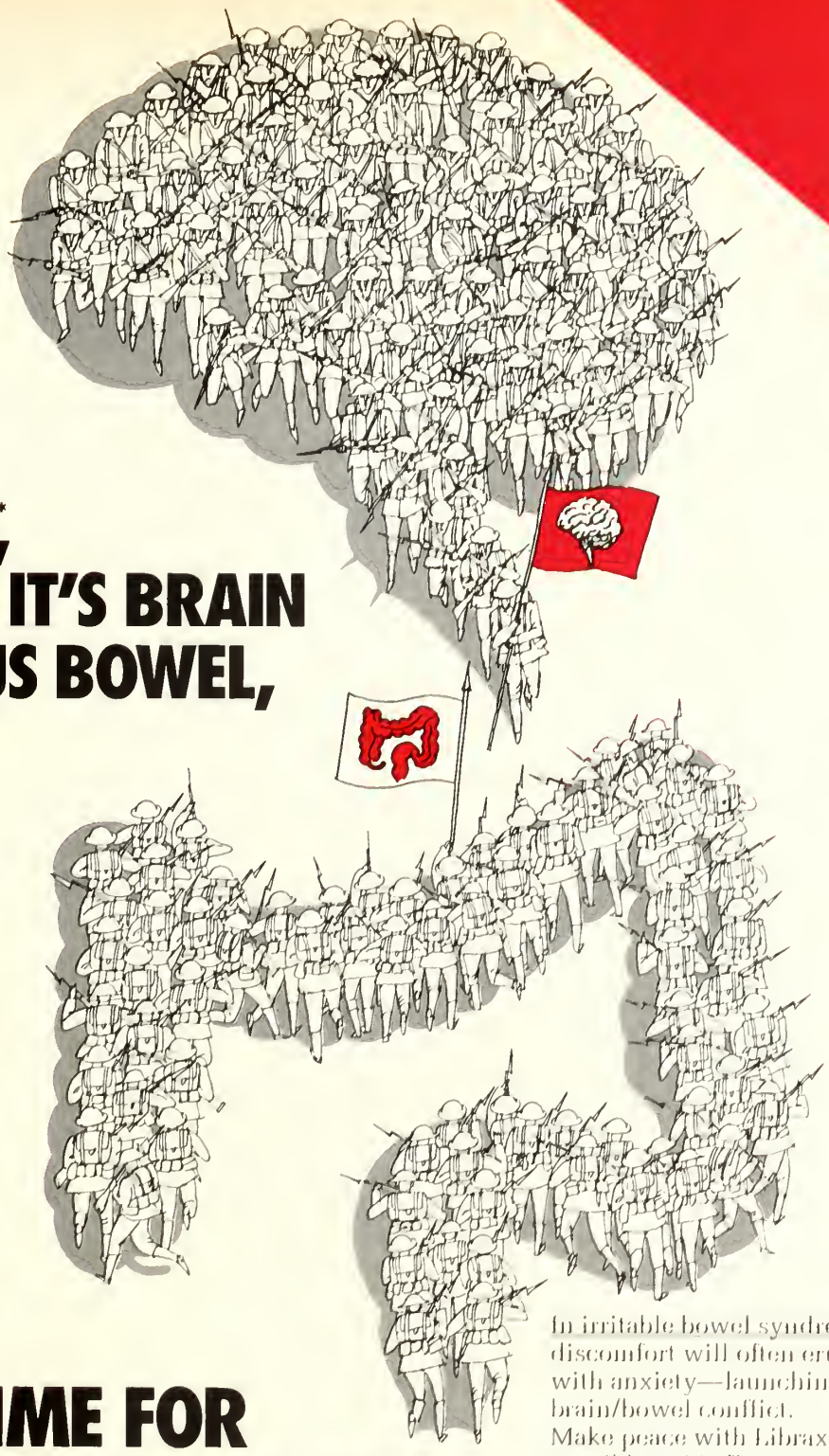

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ABSTRACTS DECEMBER 1991

(Gordon GS, Sefcik SE, LoGerfo JP: Charges for comprehensive obstetric care at teaching and nonteaching hospitals—A comparison. West J Med 1991 Dec; 155:616-620)

We compared total charges for obstetric care at a major teaching hospital and faculty group practice with those at 3 nonteaching centers in western Washington. The patients were all enrollees of an employee-based health maintenance organization. Charges were used as a proxy for costs and included all outpatient, inpatient, and physician charges. In the teaching system, patients were cared for by faculty and house staff; in the nonteaching settings, they received care from private physicians. No significant differences in total charges were found between the teaching and the nonteaching settings for all deliveries ($4,652 [N = 90] versus $4,530 [N = 335], $P > .5$). In the teaching setting, vaginal deliveries were slightly more expensive ($4,178 [n = 75] versus $3,768 [n = 250], $P = .15$), as were cesarean deliveries ($7,024 [n = 15] versus $6,771 [n = 85], $P > .5$). The rate of cesarean deliveries was lower in the teaching setting (17% versus 25%, $P = .10$), partially accounting for the similarity in total charges. The length of stay was similar in the teaching hospital (3.29 versus 3.14 days, $P > .5$). We conclude that the academic medical center as a total system of care can provide obstetric care as cost-effectively as nonteaching systems under the constraints of prepaid care.

OBSTETRICS
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Three copies of this abstract are provided to help you in filing and cross-referencing research articles.

The EXCEL Study:
48 weeks, 8,245 patients,
362 medical centers,
in the largest-ever U.S.
randomized, double-blind,
placebo-controlled
trial of patients with primary
hypercholesterolemia

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the results are in...

For a Brief Summary of Prescribing Information,
please see the last page of this advertisement.

Bradford, R.H. et al.: Expanded clinical evaluation of lovastatin (EXCEL) study results: I. Efficacy in modifying plasma lipoproteins and adverse event profile in 8,245 patients with moderate hypercholesterolemia, *Archives of Internal Medicine,* January 1991.

Lovastatin lowere
Lovastatin lowere
Lovastatin lowere
Lovastatin raised

MEVACOR® (Lovastatin, MSD) is contraindicated in patients who are hypersensitive to any component of the medication; in patients with active liver disease or unexplained persistent transaminase elevations; in pregnant or lactating patients; and in women of childbearing age, except when such patients are highly unlikely to conceive.

For complete details on MEVACOR, including cautionary information regarding myopathy, drug interactions, and liver enzyme monitoring, please refer to the Prescribing Information.

For a Brief Summary of Prescribing Information, please see the last page of this advertisement.

*Mean percent changes from baseline (n=6,582)
**Triglyceride values are median changes.
Dosage ranged from 20 mg q.p.m. to 40 mg b.i.d.

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DL cholesterol* 24-40%

tal cholesterol* 17-29%

glycerides** 10-19%

DL cholesterol* 6.6-9.5%

For many patients with primary hypercholesterolemia (Types IIa and IIb), when diet and other nondrug therapies are inadequate

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(LOVASTATIN | MSD)

TABLETS, 10 mg 20 mg 40 mg

MSD
MERCK SHARP & DOHME

MEVACOR®
(LOVASTATIN | MSD)

CONTRAINDICATIONS: Hypersensitivity to any component of this medication

Active liver disease or unexplained persistent elevations of serum transaminases

Pregnancy and lactation

Atherosclerosis is a chronic process and the discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. Moreover, cholesterol and other products of the cholesterol biosynthesis pathway are essential components for fetal development, including synthesis of steroids and cell membranes. Because of the ability of inhibitors of HMG-CoA reductase such as MEVACOR® (Lovastatin, MSD) to decrease the synthesis of cholesterol and possibly other products of the cholesterol biosynthesis pathway, MEVACOR may cause fetal harm when administered to a pregnant woman. Therefore, lovastatin is contraindicated during pregnancy. Lovastatin should be administered to women of childbearing age only when such patients are highly unlikely to conceive. If the patient becomes pregnant while taking this drug, lovastatin should be discontinued and the patient should be apprised of the potential hazard to the fetus.

WARNINGS: *Liver Dysfunction*: **Marked persistent increases (to more than 3 times the upper limit of normal) in serum transaminases occurred in 1.9% of adult patients who received lovastatin for at least one year in clinical trials (see ADVERSE REACTIONS).** When the drug was interrupted or discontinued in these patients, the transaminase levels usually fell slowly to pretreatment levels. The increases usually appeared 3 to 12 months after the start of therapy with lovastatin and were not associated with jaundice or other clinical signs or symptoms. There was no evidence of hypersensitivity.

It is recommended that liver function tests be performed during therapy with lovastatin. Serum transaminases, including ALT (SGPT), should be monitored before treatment begins, every 6 weeks for the first 3 months, every 8 weeks during the remainder of the first year, and periodically thereafter (e.g., at approximately 6-month intervals). Special attention should be paid to patients who develop elevated serum transaminase levels, and in these patients, measurements should be repeated promptly and then performed more frequently. If the transaminase levels show evidence of progression, particularly if they rise to 3 times the upper limit of normal and are persistent, the drug should be discontinued. Liver biopsy should be considered if elevations are persistent beyond the discontinuation of the drug.

The drug should be used with caution in patients who consume substantial quantities of alcohol and/or have a past history of liver disease. Active liver disease or unexplained transaminase elevations are contraindications to the use of lovastatin.

As with other lipid-lowering agents, moderate (less than 3 times the upper limit of normal) elevations of serum transaminases have been reported following therapy with MEVACOR (see ADVERSE REACTIONS). These changes appeared soon after initiation of therapy with MEVACOR, were often transient, were not accompanied by any symptoms, and interruption of treatment was not required.

Skeletal Muscle: **Rhabdomyolysis has been associated with lovastatin therapy alone, when combined with immunosuppressive therapy including cyclosporine in cardiac transplant patients, and when combined in non-transplant patients with either gemfibrozil or lipid-lowering doses (≥1 g/day) of nicotinic acid. Some of the affected patients had preexisting renal insufficiency, usually as a consequence of long-standing diabetes. Acute renal failure from rhabdomyolysis has been seen more commonly with the lovastatin-gemfibrozil combination and has also been reported in transplant patients receiving lovastatin plus cyclosporine.**

Rhabdomyolysis with or without renal impairment has been reported in seriously ill patients receiving erythromycin concomitantly with lovastatin. Therefore, patients receiving concomitant lovastatin and erythromycin should be carefully monitored.

Fulminant rhabdomyolysis has been seen as early as 3 weeks after initiation of combined therapy with gemfibrozil and lovastatin but may be seen after several months. For these reasons, it is felt that, in most subjects who have had an unsatisfactory lipid response to either drug alone, the possible benefits of combined therapy with lovastatin and gemfibrozil do not outweigh the risks of severe myopathy, rhabdomyolysis, and acute renal failure. While it is not known whether this interaction occurs with fibrates other than gemfibrozil, myopathy and rhabdomyolysis have occasionally been associated with the use of other fibrates alone, including clofibrate. Therefore, the combined use of lovastatin with other fibrates should generally be avoided.

Physicians contemplating combined therapy with lovastatin and lipid-lowering doses of nicotinic acid or with immunosuppressive drugs should carefully weigh the potential benefits and risks and should carefully monitor patients for any signs and symptoms of muscle pain, tenderness, or weakness, particularly during the initial months of therapy and during any periods of upward dosage titration of either drug. Periodic CPK determinations may be considered in such situations, but there is no assurance that such monitoring will prevent the occurrence of severe myopathy. The monitoring of lovastatin drug and metabolite levels may be considered in transplant patients who are treated with immunosuppressives and lovastatin.

Lovastatin therapy should be temporarily withheld or discontinued in any patient with an acute, serious condition suggestive of a myopathy or having a risk factor predisposing to the development of renal failure secondary to rhabdomyolysis, including severe acute infection, hypotension, major surgery, trauma, severe metabolic, endocrine, and electrolyte disorders, and uncontrolled seizures.

Myalgia has been associated with lovastatin therapy. Transient, mildly elevated creatine phosphokinase levels are commonly seen in lovastatin-treated patients. However, in clinical trials, approximately 0.5% of patients developed a myopathy, i.e., myalgia or muscle weakness associated with markedly elevated CPK levels. Myopathy should be considered in any patient with diffuse myalgias, muscle tenderness, or weakness, and/or marked elevation of CPK. Patients should be advised to report promptly unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever. Lovastatin therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected.

Most of the patients who have developed myopathy (including rhabdomyolysis) while taking lovastatin were receiving concomitant therapy with immunosuppressive drugs, gemfibrozil, or lipid-lowering doses of nicotinic acid. In clinical trials, about 30% of patients on concomitant immunosuppressive therapy including cyclosporine developed myopathy, the corresponding percentages for gemfibrozil and niacin were approximately 5% and 2%, respectively.

In 6 patients with cardiac transplants taking immunosuppressive therapy including cyclosporine concomitantly with lovastatin 20 mg/day, the average plasma level of active metabolites derived from lovastatin was elevated to approximately 4 times the expected levels. Because of an apparent relationship between increased plasma levels of active metabolites derived from lovastatin and myopathy, the daily dosage in patients taking immunosuppressants should not exceed 20 mg/day (see DOSAGE AND ADMINISTRATION). Even at this dosage, the benefits and risks of using lovastatin in patients taking immunosuppressants should be carefully considered.

PRECAUTIONS: *General*: Before instituting therapy with MEVACOR, an attempt should be made to control hypercholesterolemia with appropriate diet, exercise, weight reduction in obese patients, and to treat other underlying medical problems (see INDICATIONS AND USAGE).

Lovastatin may elevate creatine phosphokinase and transaminase levels (see ADVERSE REACTIONS). This should be considered in the differential diagnosis of chest pain in a patient on therapy with lovastatin.

Homozygous Familial Hypercholesterolemia: MEVACOR® (Lovastatin, MSD) is less effective in patients with the rare homozygous familial hypercholesterolemia, possibly because these patients have no functional LDL receptors. MEVACOR appears to be more likely to raise serum transaminases (see ADVERSE REACTIONS) in these homozygous patients.

Drug Interactions: *Immunosuppressive Drugs, Gemfibrozil, Niacin (Nicotinic Acid), Erythromycin*: See WARNINGS, *Skeletal Muscle*.

Coumarin Anticoagulants: In a clinical trial in warfarin-treated patients designed specifically to observe a potential effect of lovastatin on the prothrombin time, lovastatin in dosages up to 40 mg b.i.d. did not produce any consistent alteration of the anticoagulant action of warfarin. However, since the drug was marketed, clinically evident bleeding and/or increased prothrombin time have been reported in a few patients taking coumarin anticoagulants concomitantly with lovastatin. The causal relationship to lovastatin is unclear. Nevertheless, it is recommended that in patients taking anticoagulants, prothrombin time be determined before starting lovastatin and frequently enough during early therapy to insure that no significant alteration of prothrombin time occurs. Once a stable prothrombin time has been documented, prothrombin times can be monitored at the intervals usually recommended for patients on coumarin anticoagulants. If the dose of lovastatin is changed, the same procedure should be repeated. Lovastatin therapy has not been associated with bleeding or with changes in prothrombin time in patients not taking anticoagulants.

Antipyrine: Antipyrine is a model for drugs metabolized by the microsomal hepatic enzyme system (cytochrome P450 system). Because lovastatin had no effect on the pharmacokinetics of antipyrine, interactions with other drugs metabolized via this mechanism are not expected.

Propranolol: In normal volunteers, there was no clinically significant pharmacokinetic or pharmacodynamic interaction with concomitant administration of single doses of lovastatin and propranolol.

Digoxin: In patients with hypercholesterolemia, concomitant administration of lovastatin and digoxin resulted in no effect on digoxin plasma concentrations.

Other Concomitant Therapy: Although specific interaction studies were not performed, in clinical studies, lovastatin was used concomitantly with beta blockers, calcium channel blockers, diuretics, and nonsteroidal anti-inflammatory drugs (NSAIDs) without evidence of clinically significant adverse interactions.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a 21-month carcinogenic study in mice, a statistically significant ($p < 0.05$) increase in the incidence of hepatocellular carcinomas and adenomas was observed at doses of 500 mg/kg/day (312 times the maximum recommended human dose) of lovastatin. These changes were not seen in mice given doses of 20 and 100 mg/kg/day (12.5 and 62.5 times the maximum recommended human dose).

A statistically significant increase ($p \leq 0.05$) in the incidence of pulmonary adenomas was seen in female mice receiving 500 mg/kg/day (312 times the maximum recommended human dose). No similar changes were seen in males at any dose or in females receiving 20 or 100 mg/kg/day (12.5 or 62.5 times the maximum recommended human dose). Because the incidence of pulmonary tumors was within the range of untreated animals in studies of similar duration, the relationship of this latter change to treatment is not known.

In addition, an increase in the incidence of papilloma in the non-glandular mucosa of the stomach was observed in mice receiving 100 and 500 mg/kg/day (62.5 and 312 times the maximum recommended human dose), no increase was seen at a dosage of 20 mg/kg/day (12.5 times the maximum recommended human dose). The glandular mucosa was not affected. The human stomach contains only glandular mucosa. Importantly, there is a strong association between this change and hyperplasia of the squamous epithelium (acanthosis) in this region, acanthosis is a characteristic change observed in the non-glandular mucosa of rodents treated with HMG-CoA reductase inhibitors and is most probably a result of inhibition of the reductase in this tissue.

Similar squamous epithelium is found in the esophagus and anorectal junction of the mouse and rat; however, no evidence of a similar drug-induced hyperplastic response was observed in these tissues in studies of up to 21 months in the mouse given up to 500 mg/kg/day (312 times the maximum recommended human dose), or in a study of 24 months in the rat given 180 mg/kg/day (112 times the maximum recommended human dose).

In a 24-month carcinogenicity study in rats, there was a positive dose response relationship for hepatocellular carcinogenicity in males (unadjusted $p = 0.025$). However, because the incidence of hepatocellular carcinogenicity observed in male rats in this study is similar to that observed spontaneously in this strain of rat, the implications of this finding are unclear.

Drug-related testicular atrophy, decreased spermatogenesis, spermatocytic degeneration and giant cell formation were seen in dogs starting at 20 mg/kg/day (12.5 times the maximum recommended human dose). The clinical significance of these findings is unclear.

No evidence of mutagenicity was observed in a microbial mutagen test using mutant strains of *Salmonella typhimurium* with or without rat or mouse liver metabolic activation. In addition, no evidence of damage to genetic material was noted in an *in vitro* alkaline elution assay using rat or mouse hepatocytes, a V-79 mammalian cell forward mutation study, an *in vitro* chromosome aberration study in CHO cells, or an *in vivo* chromosomal aberration assay in mouse bone marrow.

No drug-related effects on fertility were found in studies with rats.

Pregnancy: Pregnancy Category X. See CONTRAINDICATIONS.

Lovastatin has been shown to produce skeletal malformations in the rat fetus at doses of 800 mg/kg/day (500 times the maximum recommended human dose). At similar doses in mice, an increase in skeletal malformations was observed. These individual changes are within the range of those observed spontaneously in this strain of mouse. No drug-induced changes were seen in either species at doses of up to 80 mg/kg/day (50 times the maximum recommended human dose). No evidence of malformations was noted in rabbits at up to 15 mg/kg/day (highest tolerated dose—about 9 times the maximum recommended human dose). There are no data in pregnant women.

Nursing Mothers: Studies in rats have shown that lovastatin is excreted in the milk. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from MEVACOR, women taking lovastatin should not nurse their infants (see CONTRAINDICATIONS).

Pediatric Use: Safety and effectiveness in children have not been established. Because children are not likely to benefit from cholesterol lowering for at least a decade and because experience with this drug is limited (no studies in subjects below the age of 20 years), treatment of children with lovastatin is not recommended at this time.

ADVERSE REACTIONS: MEVACOR is generally well tolerated, adverse reactions usually have been mild and transient. Less than 1% of patients were discontinued from controlled clinical studies due to adverse experiences attributable to MEVACOR. About 2% of patients were discontinued from all studies (controlled and uncontrolled) due to adverse experiences attributable to MEVACOR, about one-third of these patients were discontinued due to increases in serum transaminases.

Clinical Adverse Experiences: Adverse experiences reported in pa treated with MEVACOR® (Lovastatin, MSD) in controlled clinical st are shown in the table below.

	MEVACOR (N = 613) %	Placebo (N = 82) %	Cholestyramine (N = 88) %	Pre (N
Gastrointestinal				
Constipation	4.9	—	34.1	
Diarrhea	5.5	4.9	8.0	
Dyspepsia	3.9	—	13.6	
Flatus	6.4	2.4	21.6	
Abdominal pain/cramps	5.7	2.4	5.7	
Heartburn	1.6	—	8.0	
Nausea	4.7	3.7	9.1	
Musculoskeletal				
Muscle cramps	1.1	—	1.1	
Myalgia	2.4	1.2	—	
Nervous System/Psychiatric				
Dizziness	2.0	1.2	—	
Headache	9.3	4.9	4.5	
Skin				
Rash/pruritus	5.2	—	4.5	
Special Senses				
Blurred vision	1.5	—	1.1	
Dysgeusia	0.8	—	1.1	

Laboratory Tests: Marked persistent increases of serum transami have been noted (see WARNINGS).

About 11% of patients had elevations of creatine phosphokinase levels of at least twice the normal value on one or more occasions corresponding values for the control agents were cholestyramine, 9 probucol, 2%. This was attributable to the noncardiac fraction of Large increases in CPK have sometimes been reported (see WARNI *Skeletal Muscle*).

Concomitant Therapy: In controlled clinical studies in which lova was administered concomitantly with cholestyramine, no adverse tions peculiar to this concomitant treatment were observed. The ad reactions that occurred were limited to those reported previously lovastatin or cholestyramine. Other lipid-lowering agents were not ad istered concomitantly with lovastatin during controlled clinical studi uncontrolled clinical studies, most of the patients who have deve myopathy were receiving concomitant therapy with immunosuppre drugs, gemfibrozil, or niacin (nicotinic acid) (see WARNINGS, *Sk Muscle*).

Uncontrolled Clinical Studies: The adverse experiences observ uncontrolled studies were similar to those seen in controlled c studies. Abnormal liver function tests were observed at a higher inci than in the controlled studies (see WARNINGS, *Liver Dysfunction*). T athy (myalgia with marked CPK elevations) was reported in ap imately 0.5% of patients (see WARNINGS, *Skeletal Muscle*).

Causal Relationship Unclear: *Nervous System*: Peripheral neuro has been reported, the relationship to lovastatin is uncertain. evoked response, nerve conduction measurements, and electromy phy in over 30 patients showed no evidence of neurotoxic effe lovastatin.

Eye: Lens opacities (see CLINICAL PHARMACOLOGY, *Clinical Stu*

Post-marketing Experience: Additional adverse experiences occ since the drug was marketed are listed below.

Clinical Adverse Experiences

Gastrointestinal: Hepatitis, chronic active hepatitis, chole jaundice, fatty change in liver, and, rarely fulminant hepatic necrosi rhosis, and hepatoma, anorexia, vomiting.

Hypersensitivity Reactions: An apparent hypersensitivity syndr has been reported rarely which has included one or more of the follo features: anaphylaxis, angioedema, lupus-like syndrome, polym rheumatica, vasculitis, thrombocytopenia, leukopenia, hemolytic mia, positive ANA, ESR increase, arthritis, arthralgia, urticaria, asth photosensitivity, fever, chills, flushing, malaise, and dyspnea.

Nervous System/Psychiatric: Psychic disturbances, incl anxiety, paresthesia.

Skin: Erythema multiforme, including Stevens-Johnson drome, toxic epidermal necrolysis.

Causal Relationship Unknown

Eye: Progression of cataracts (lens opacities).

Gastrointestinal: Pancreatitis, stomatitis.

Skin: Alopecia.

Nervous System/Psychiatric: Depression, insomnia.

Metabolic: Edema.

Clinical Laboratory Test Findings

Liver Function Tests: Liver function test abnormalities, incl elevated alkaline phosphatase and bilirubin.

Thyroid Function Tests: Rare reports of thyroid function test a malities in patients taking concomitant thyroxine.

OVERDOSAGE: The oral LD_{50} of MEVACOR in mice is 20 g/kg.

Five healthy human volunteers have received up to 200 mg of lova as a single dose without clinically significant adverse experiences. cases of accidental overdosage have been reported, no patients ha specific symptoms, and all patients recovered without sequelae. The imum dose taken was 5 to 6 g.

Until further experience is obtained, no specific treatment of ove age with MEVACOR can be recommended.

The dialyzability of lovastatin and its metabolites in man is not kno present.

DOSAGE AND ADMINISTRATION: The patient should be placed on a dard cholesterol-lowering diet before receiving MEVACOR and s continue on this diet during treatment with MEVACOR. MEVACOR s be given with meals.

The recommended starting dose is 20 mg once a day given wi evening meal. The recommended dosing range is 20 to 80 mg/day gle or divided doses, the maximum recommended dose is 80 m Adjustments of dosage should be made at intervals of 4 weeks or Doses should be individualized according to the patient's respons Tables I to IV under CLINICAL PHARMACOLOGY, *Clinical Studies* for response results).

For those patients with severely elevated serum cholesterol (i.e., ≥300 mg/dL [7.8 mmol/L] on diet), MEVACOR may be initiated mg/day.

In patients taking immunosuppressive drugs concomitantly lovastatin (see WARNINGS, *Skeletal Muscle*), therapy should begi 10 mg of MEVACOR and should not exceed 20 mg/day.

Cholesterol levels should be monitored periodically and conside should be given to reducing the dosage of MEVACOR if cholesterol fall below the targeted range.

Concomitant Therapy: Preliminary evidence suggests that the c terol-lowering effects of lovastatin and the bile acid sequestrant, c tyramine, are additive.

Dosage in Patients with Renal Insufficiency: In patients with severe insufficiency (creatinine clearance < 30 mL/min), dosage increases above 20 mg/day should be carefully considered and, if deemed necessary, implemented cautiously (see CLINICAL PHARMACOLOGY and WARNINGS, *Skeletal Muscle*).

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ALLERGY

February 6-8—**Allergy Diagnosis.** UCSD at La Jolla Village Inn. Thurs-Sat. 20 hrs. $290. Contact: Janice Turner, PO Box 2586, La Jolla 92038. (619) 459-1564.

March 27-28—**Asthma and Allergy in the 1990s.** Medical Education Resources at Wyndham Hotel, Palm Springs. Fri-Sat. Contact: MER, 1500 W Canal Ct, Ste 500, Littleton, CO 80120. (800) 421-3756.

ANESTHESIOLOGY

January 9-12—**UCSD Anesthesia Update: 1992.** UCSD at Hotel del Coronado, San Diego. Thurs-Sun. Contact: UCSD.

January 19-21—**Second America-Japan Anesthesia Congress.** International Anesthesia Research Society at Sheraton Waikiki Hotel, Honolulu, Hawaii. Sun-Tue. 14 hrs. $250. Contact: Vicky Larsen, University of Utah School of Medicine, 50 North Medical Drive, Salt Lake City, UT 84132. (801) 581-6115.

January 19-24—**Hawaiian Seminar on Clinical Anesthesia.** California Society of Anesthesiologists at Westin Maui Hotel, Kaanapali Beach, Maui, Hawaii. Sun-Fri. 20 hrs. Contact: California Society of Anesthesiologists, 1065 E Hillsdale Blvd, #410, Foster City 94404. (800) 345-3691.

January 24-26—**30th Clinical Conference in Pediatric Anesthesiology.** Children's Hospital of Los Angeles at Stouffer Concourse Hotel. Fri-Sun. 15 hrs. Contact: Katherine Barky, MD, PO Box 54700, Los Angeles 90054. (213) 669-2262.

March 13-17—**66th Congress of the International Anesthesia Research Society.** International Anesthesia Research Society at San Francisco Hilton & Towers. Fri-Tues. Contact: Anne Maggiore, IARS, 2 Summit Park Dr, Ste 140, Cleveland, OH 44131. (216) 642-1124.

March 21-22—**Postgraduate Assembly.** Los Angeles County Society of Anesthesiologists at Sheraton Universal Hotel, Universal City. Sat-Sun. Contact: Michael Carlson, 1903 Redondo Ave, Long Beach 90804. (213) 597-2661.

March 21-26—**20th Obstetric Anesthesia Conference.** Ohio State University Hospitals at Sheraton Waikiki Hotel, Honolulu, Hawaii. Sat-Thurs. Contact: Arlene Rogers, 410 W 10th Ave, Columbus, OH 43210. (614) 293-8487.

May 17-22—**Anesthesiology Review Course.** UCSD at San Diego Princess Resort. Sun-Fri. Contact: UCSD.

CARDIOLOGY

January 18-25—**Cardiopulmonary Emergencies.** UCSD at Kona, Hawaii. 1 week. Contact: UCSD.

February 14-16—**Arrhythmias: Interpretation, Diagnosis and Management.** Medical Education Resources at Disneyland Hotel, Anaheim. Fri-Sun. Contact: MER, 1500 W Canal Ct, Ste 500, Littleton, CO 80120. (800) 421-3756.

March 20-21—**Cardiac Diagnostic Methods & Risk Management.** Medical Education Resources at Caesars Palace, Las Vegas, Nevada. Fri-Sat. Contact: MER, 1500 W Canal Ct, Ste 500, Littleton, CO 80120. (800) 421-3756.

April 4—**Practical Cardiology for the '90s.** Grossmont Hospital at La Mesa. Sat. Contact: Karen Hamilton, PO Box 158, La Mesa 91944-0158. (619) 589-4168.

April 6-11—**31st Annual Cardiology Retreat.** Scripps Clinic and Research Foundation at Rancho Santa Fe. Mon-Sat. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

April 21-23—**2nd Annual Symposium on Coronary Stenting: A Live Demonstration Course.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Tues-Thurs. 18 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

May 1-2—**2nd International Symposium on Thrombolytic Therapy in Acute Ischemic Stroke.** Scripps Clinic and Research Foundation at San Diego Marriott, La Jolla. Fri-Sat. Contact: Scripps Clinic, Box 403C, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

CRITICAL CARE

February 3-7—**Critical Care Medicine.** USC at Caesar's Palace, Las Vegas, Nevada. Mon-Fri. 33.5 hrs. $695. Contact: USC.

DERMATOLOGY

January 17-19—**Practical Dermatology and Dermatologic Office Procedures for the Primary Care Physician.** UCSD at Hyatt Regency, La Jolla. Fri-Sun. 20 hrs. Contact: Jacqueline Shiller, Box 84296, San Diego 92138. (619) 223-2997.

January 31-February 2—**Cutaneous Malignancies: 1992 Skin Cancer Update.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Fri-Sun. 18 hrs. Contact: Susan Buntjer, Scripps Clinic and Research Foundation, 10666 N Torrey Pines Road, La Jolla 92037. (619) 554-8556.

February 27—**Problems of the Aging Skin.** Stanford Medical Center at Palm Springs. Thurs-Sun. Contact: Pamela Bain, R-144, Stanford 94305. (415) 723-7854.

KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690. (415) 541-0900.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Herbert M. Thomas, MD, MPH, Director of CME, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th St, Los Angeles 90059. (213) 603-3183.

LLU: Loma Linda University
Contact: James J. Couperus, MD, Associate Dean for Educational Affairs, Loma Linda University School of Medicine, Loma Linda 92350.

PMC: Pacific Medical Center
Contact: Continuing Education, Pacific Medical Center, PO Box 7999, San Francisco 94120. (415) 563-4321, ext 2761.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Medical School Office Building, Suite X-365, Stanford 94305-6114. (415) 723-5594.

UCD: University of California, Davis
Contact: Ruth Feryok, Director, Office of Continuing Medical Education, University of California, Davis, School of Medicine, 2701 Stockton Blvd, Sacramento 95817. (916) 734-5390.

UCI: University of California, Irvine
Contact: Melvin I. Marks, MD, Director, Memorial/UCI Center for Health Education, Long Beach Memorial Medical Center, 2801 Atlantic Ave, PO Box 1428, Long Beach, California 90801-1428. (213) 595-3811.

UCLA: University of California, Los Angeles Extension
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, PO Box 24902, UCLA, Los Angeles 90024. (213) 825-8423.

UCSD: University of California, San Diego
Contact: Office of Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (619) 534-3940.

UCSF: University of California, San Francisco
Contact: Janet Johnson, Administrative Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 476-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 1975 Zonal Ave, KAM314, Los Angeles 90033. (800) 872-1119.

(Continued on Page 600)

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ACP Membership: Consult your Advance Program mailed in December. It contains information about the meeting and how to register.

Nonmembers: Watch for the complete schedule of events and a registration form in the Annual Session Digest appearing in the December 15, 1991, and January 1 and February 1, 1992, issues of *Annals of Internal Medicine*.

ACP

CONTINUING MEDICAL EDUCATION

(Continued from Page 598)

EMERGENCY MEDICINE

January 10-11—**California Trauma Conference.** UCD at Hyatt Regency, Sacramento. Fri-Sat. Contact: UCD.

January 13-17—**Emergency Medicine Symposia I.** UCSD at San Diego Hilton Beach & Tennis Resort. Mon-Fri. Contact: UCSD.

February 23-28—**Emergency Medicine.** UCD at Incline Village, Nevada. Sun-Fri. Contact: UCD.

March 8-13—**13th Annual Mammoth Mountain Emergency Medicine Ski Conference.** CAL/ACEP and Orange County Emergency Department at Mammoth Lakes. Sun-Fri. 18 hrs. $395. Contact: Mark Song, Medical Conferences, PO Box 52-B, Newport Beach 92662. (714) 552-0831.

March 16-20—**Emergency Medicine Symposia II.** UCSD at Basic Science Building. Mon-Fri. Contact: UCSD.

April 1-4—**8th Annual Advances in Emergency Medicine.** UCSF at Pan Pacific Hotel, San Francisco. Wed-Sat. $455. Contact: UCSF.

May 6-10—**14th Biannual: Wound Management Workshop.** UCSD at San Diego Hilton Beach & Tennis Resort. Wed-Sun. 18 hrs. $200-$435. Contact: UCSD.

May 11-15—**Emergency Medicine Symposia I.** UCSD at San Diego Hilton Beach & Tennis Resort. Mon-Fri. Contact: UCSD.

ENDOCRINOLOGY AND METABOLISM

March 4-5—**Advances in Endocrinology and Metabolism.** UCSF at Pan Pacific Hotel, San Francisco. Wed-Thurs. 14.5 hrs. $295. Contact: UCSF.

March 6—**18th Annual Diabetes Symposium.** UCD at Sacramento. Fri. 6 hrs. $140. Contact: UCD.

March 6-7—**Diabetes Update.** UCSF at Pan Pacific Hotel, San Francisco. Fri-Sat. 10 hrs. $245. Contact: UCSF.

FAMILY PRACTICE/PRIMARY CARE

February 9-15—**UCI Family Practice Refresher Course.** Memorial/UCI Center for Health Education at Marriott Hotel, Newport Beach. Sun-Sat. Contact: UCI.

February 13-15—**Current Concepts in Cancer Management: A Symposium for Primary Care Physicians and Cancer Care Providers.** Hoag Memorial Center at Newport Beach Marriott. Thurs-Sat. $350. Contact: Meeting Management, 5665 Oberlin, Ste 110, San Diego 92121. (619) 453-6222.

February 13-16—**44th Annual Scientific Assembly.** California Academy of Family Physicians at Sheraton Harbor Island Hotel, San Diego. Thurs-Sun. 26 hrs. $275. Contact: Robert Fagan, CAFP, 114 Sansome St, Ste 1305, San Francisco 94104. (415) 394-9121.

February 14-16—**Office Gynecology for the Primary Care Physician.** SDSU at Hyatt Islandia, San Diego. Fri-Sun. 20 hrs. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

February 17-19—**Issues in Men's Health.** SDSU at Hyatt Islandia, San Diego. Mon-Wed. 20 hrs. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

March 25-27—**Annual Review in Family Medicine: Controversies and Challenges in Primary Care.** UCSF. Wed-Fri. 15.5 hrs. Contact: UCSF.

April 4—**Cardiology for Primary Care.** UCDMC at Cancer Center Auditorium. Sat. Contact: UCD.

April 4-11—**5th Annual Primary Care Medicine: Update 1992.** UCSF at Maui Intercontinental, Wailea, Maui, Hawaii. 1 week. $540. Contact: UCSF.

April 9-11—**Advances in Rheumatology for Primary Care Physicians.** UCSF at Le Meridien Hotel, San Francisco. Thurs-Sat. $240. Contact: UCSF.

April 10—**Office Orthopedics for the Primary Care Physician.** Sharp Memorial Hospital at San Diego Princess Vacation Village, San Diego. Fri. 20 hrs. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

GASTROENTEROLOGY

February 29-March 1—**Endoscopy Update 1992.** Southern California Society for Gastroenterology at Century Plaza Hotel, Los Angeles. Sat-Sun. Contact: Joyce Fried, University of California Brain Research Institute, Los Angeles 90024.

GERIATRICS

January 21-25—**9th UCLA Intensive Course in Geriatric Medicine.** UCLA at Beverly Hilton. Tues-Sat. 40 hrs. $600. Contact: UCLA.

January 24-25—**Alzheimer's Disease: New Approaches to Treatment.** UCSD at Westgate Hotel, San Diego. Contact: Cass Jones, Professional Conference Management, 7916 Convoy Ct, San Diego 92111. (619) 565-9921.

March 6-8—**Recent Advances in Geriatric Medicine-Healthy People 2000: A New Look at Screening, Prevention and Rehabilitation in the Elderly.** UCSD at Pan Pacific Hotel, San Diego. Fri-Sun. Contact: Cass Jones, Professional Conference Management, 7916 Convoy Ct, San Diego 92111. (619) 565-9921.

March 16-17—**Exercise in Geriatric Care.** VA Sepulveda Medical Center at Burbank. Mon-Tues. Contact: Symposium Secretary, VA Medical Center, GRECC (11E), 16111 Plummer St, Sepulveda 91343. (818) 895-9311.

INFECTIOUS DISEASES

February 7-8—**10th Annual Practical Update of Infectious Disease.** UCD. Fri-Sat. 12 hrs. $160. Contact: UCD.

April 25—**HIV Update.** UCDMC at Cancer Center Auditorium. Sat. Contact: UCD.

April 29-May 1—**13th Annual Advances in Infectious Diseases.** UCSF at San Francisco. Wed-Fri. $400. Contact: UCSF.

May 6-8—**13th Annual Advances in Infectious Diseases.** UCSF at Sheraton Palace Hotel, San Francisco. Wed-Fri. $400. Contact: UCSF.

INTERNAL MEDICINE

January 30-February 1—**Advanced Nephrology: Nephrology for the Consultant.** UCSD at La Jolla Marriott, San Diego. Thurs-Sat. 17 hrs. $350. Contact: UCSD.

February 22-27—**Topics and Advances in Internal Medicine.** UCSD at Sheraton Harbor Island, San Diego. Sat-Sun. Contact: UCSD.

February 23-25—**5th Annual Congress of the North American Society of Phlebology on the Advances in Sclerotherapy and the Advances in Surgical and Medical Treatment of Venous Disease.** North American Society of Phlebology and the American Academy of Dermatology at Grand Hyatt Union Square, San Francisco. Sun-Tues. 14 hrs. Contact: NASP, 204 N El Camino Real, E-234, Encinitas 92024. (619) 942-8380.

February 27-29—**1992 Zimmerman Conference: Progress in Vascular Biology, Hemostasis and Thrombosis.** Scripps Clinic at Sheraton Grande Torrey Pines Hotel, La Jolla. Thurs-Sat. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

March 20-26—**Internal Medicine 1992: A Comprehensive Review.** Sharp Memorial Hospital at Hotel del Coronado. Fri-Thurs. 54 hours. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

May 11-15—**20th Annual Advances in Internal Medicine.** UCSF at Ritz-Carlton Hotel, San Francisco. Mon-Fri. 33 hrs. $610. Contact: UCSF.

NEUROLOGY

January 30-February 1—**15th Annual: Neurology for Non-Neurologists.** UCSD at Omni San Diego Hotel. Thurs-Sat. 21 hrs. $375. Contact: UCSD.

February 13-15—**25th Annual Recent Advances in Neurology.** UCSF at San Francisco. Thurs-Sat. 15 hrs. Contact: UCSF.

OB/GYN

January 16-19—**OB/GYN and Ultrasound.** UCSD at Hotel del Coronado, San Diego. Thurs-Sun. 20 hrs. $450. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

February 2-6—**Ambulatory Gynecology.** UCD at Hyatt Lake Tahoe, Incline Village, Nevada. Sun-Thurs. Contact: UCD.

February 13-16—**47th Annual Postgraduate Assembly.** OB/GYN Assembly of Southern California at Beverly Hilton, Beverly Hills. Thurs-Sun. 28 hrs. Contact: OB/GYN Assembly, 5820 Wilshire Blvd, #500, Los Angeles 90036. (213) 937-5514.

April 2-4—**Gynecologic Surgery.** Memorial/UCI Center for Health Education at Marquis Hotel, Palm Springs. Thurs-Sat. Contact: UCI.

April 2-4—**Ultrasound Update.** Memorial/UCI Center for Health Education at Bally's Hotel, Las Vegas. Thurs-Sat. Contact: UCI.

(Continued on Page 602)

Annual Session and | Western Scientific Assembly | March 13-18, 1992 Disneyland Hotel Anaheim, CA

California Medical Association

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House of Delegates will set CMA policy on health care issues facing physicians.

For complete program and registration information call (415) 882-3384 or MAIL this form to: California Medical Association, Attention: Anna Durante, P.O. Box 7690, San Francisco, CA 94120-7690

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Hospital Medical Staff Section and **Young Physicians Section** will convene their annual meetings.

Technical Exhibits will feature medical and other health care related exhibits.

Special Events will include a tour of Universal Studios and Hollywood, Laguna Arts and Antiques, Whale Watching and much more.

CONTINUING MEDICAL EDUCATION

(Continued from Page 600)

April 8-12—**Pacific Coast Fertility Society: Annual Scientific Program and Postgraduate Course.** Pacific Coast Fertility Society at Stouffer Esmeralda Resort, Indian Wells. Wed-Sun. 22 hrs. Contact: Director of Medical Education, 12760 La Mirada Blvd, Ste 220, La Mirada 90638. (213) 947-7068.

OCCUPATIONAL/ENVIRONMENTAL

January 27-February 7—**Occupational and Environmental Medicine Series: Session I.** UCSF at Miyako Hotel, San Francisco. Mon-Fri. 80 hrs. $1200. Contact: UCSF.

February 10-14—**Occupational and Environmental Medicine: Session III.** UCSF at Miyako Hotel Japan Center, San Francisco. Mon-Fri. 40 hrs. $600. Contact: UCSF.

February 12-16—**Team Physician Course.** American College of Sports Medicine at Wyndham Hotel, Palm Springs. Wed-Sun. Contact: ACMS, PO Box 1440, Indianapolis, IN 46202-1440. (317) 637-9200.

ONCOLOGY

February 17-19—**Clinical Hematology and Oncology: 1992.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Mon-Wed. 18 hrs. $385. Contact: Susan Buntjer, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

February 29—**Neo Adjuvant Approach to Non-Small Cell Lung Cancer.** UCD at Incline Village, Nevada. Sat. Contact: UCD.

March 5-7—**7th International Conference on Monoclonal Antibody Immunoconjugates for Cancer.** UCSD at San Diego Marriott. Thurs-Sat. Contact: UCSD.

April 30-May 3—**Breast Cancer Conference.** Memorial/UCI Center for Health Education at Hyatt Regency, Long Beach. Thurs-Sun. Contact: UCI.

OPHTHALMOLOGY

January 31-February 4—**11th Annual Squaw Valley Retina Symposium.** Alta-California Ophthalmological Society at Resort at Squaw Creek, Olympic Valley. Fri-Tues. 16 hrs. Contact: Richard Murray, 2701 Eye St, Sacramento 95816. (916) 442-4975.

May 15-16—**Pearls of Ocular Therapy.** Scripps Clinic and Research Foundation at La Jolla. Fri-Sat. Contact: Scripps Clinic, 403C, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

ORTHOPEDICS

January 23-25—**Orthopaedic Update II: Current Concepts and Advances.** UCSD at Hyatt Islandia Hotel, San Diego. Thurs-Sat. Contact: UCSD.

January 23-26—**Fracture Management.** UCD at Resort at Squaw Creek, Squaw Valley. Thurs-Sun. Contact: UCD.

March 15-20—**The Spine: Current Concepts of Diagnosis and Treatment.** Vanderbilt University Medical Center Department of Orthopaedics at Grand Hyatt Wailea, Maui, Hawaii. Sun-Fri. $575. Contact: The Spine/Current Concepts, c/o Unconventional Inc, 3960 Park Blvd, Ste E, San Diego 92103. (619) 692-9115.

PAIN MANAGEMENT

February 19-22—**The Practicing Physician's Approach to the Difficult Headache Patient.** University of Chicago School of Medicine at Wyndham Hotel, Palm Springs. Wed-Sat. 15 hrs. Contact: Idell Applebaum, Diamond Headache Clinic, 5252 N Western Ave, Chicago, IL 60625. (312) 878-0396.

PATHOLOGY

January 10-11—**Pathology Update.** UCD at Cancer Center Auditorium. Fri-Sat. Contact: UCD.

April 11—**7th Annual Conference: New Treatment in Chronic Liver Disease.** Scripps Clinic and Research Foundation at La Jolla. Sat. 6 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

PEDIATRICS

January 22-25—**San Diego Conference on Responding to Child Maltreatment.** Children's Hospital at Hyatt Regency Hotel, La Jolla. Wed-Sat. Contact: Children's Hospital, 8001 Frost St, San Diego 92123. (619) 495-4940.

February 7-9—**Current Concepts in Pediatric Medicine: 1992.** Children's Hospital San Diego at Hyatt Islandia Hotel, San Diego. Fri-Sun. 18 hrs. Children's Hospital, (619) 576-4072.

March 4-6—**17th Annual Care of the Sick Newborn.** Memorial/UCI Center for Health Education at Long Beach. Wed-Fri. Contact: UCI.

May 14-16—**25th Annual Advances and Controversies in Clinical Pediatrics.** UCSF at Fairmont Hotel, San Francisco. Thurs-Sat. Contact: UCSF.

PSYCHIATRY

January 26-31—**18th Annual Midwinter Program for Psychiatrists.** UCD at Hyatt Lake Tahoe. Sun-Fri. 25 hrs. $395. Contact: UCD.

February 1-3—**West Coast Neuropsychological Assessment Conference: Recent Advances in the Boston Approach to Neuropsychological Assessment.** UCSD at Pan Pacific Hotel, San Diego. Sun-Mon. Contact: Cass Jones, Professional Conference Management, 7916 Convoy Ct, San Diego 92111. (619) 565-9921.

February 8-9—**Breakthroughs in Anxiety Disorders: Treating Anxiety, Panic and Obsessive-Compulsive Disorders and Depression.** UCSD at Omni Hotel, San Diego. Sat-Sun. Contact: Cass Jones, Professional Conference Management, 7916 Convoy Ct, San Diego 92111. (619) 565-9921.

February 15-16—**Victims of Abuse: The Emotional Impact of Child and Adult Trauma.** San Diego Psychoanalytic Society and Institute at Hyatt Regency La Jolla at Aventine. Sat-Sun. Contact: Cass Jones, Professional Conference Management, 7916 Convoy Ct, San Diego 92111. (619) 565-9921.

March 13-15—**West Coast Psychiatry Board Review: Preparation for Part II.** UCSD at US Grant Hotel, San Diego. Fri-Sun. Contact: Cass Jones, Professional Conference Management, 7916 Convoy Ct, San Diego 92111. (619) 565-9921.

April 10-11—**The Cutting Edge 1992: Erotic Mysteries—Intimacy, Sexuality and Gender in the '90s.** UCSD at Omni Hotel, San Diego. Fri-Sat. Contact: Cass Jones, Professional Conference Management, 7916 Convoy Ct, San Diego 92111. (619) 565-9921.

April 10-14—**The Power of the Art—Suggestive Therapeutics: An Introduction to Medical Hypnosis.** UCSD at Mission Bay Hilton, San Diego. Fri-Tues. Contact: UCSD.

April 23-24—**11th Annual Conference on Child Abuse and Neglect.** UCDMC at Radisson Hotel, Sacramento. Thurs-Fri. 12 hrs. $175. Contact: UCD.

RADIOLOGY

January 10-12—**Advanced Seminars in Diagnostic Imaging.** UCSD at Ritz-Carlton Resort Hotel, Laguna Niguel. Fri-Sun. 15 hrs. $400. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925 (404) 641-9773.

January 12-16—**Diagnostic Imaging Update: Body Imaging, Mammography, Neuroradiology and Pediatrics.** Stanford University Medical Center at Ritz-Carlton Palm Beach. Sun-Thurs. 23.5 hrs. $550. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

January 31-February 2—**44th Annual Midwinter Radiological Conference.** Los Angeles Radiological Society at Century Plaza Hotel, Los Angeles. Fri-Sun. 17.25 hrs. $425. Contact: LARS, PO Box 91215, Los Angeles 90009-1215. (213) 827-9078.

February 4-7—**Advanced Seminars in Diagnostic Imaging.** UCSD at Le Meridien Hotel, Coronado. Tues-Fri. 20 hrs. $500. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

February 4-8—**18th Annual Mid-Pacific Radiological Conference.** Los Angeles Radiological Society at Hyatt Regency Waikoloa, Hawaii. Tues-Sat. 18.5 hrs. $550. Contact: LARS, PO Box 91215, Los Angeles 90009-1215. (213) 827-9078.

February 10-13—**Mammographically Detected Early Breast Cancer.** University of Alabama at Birmingham at Ritz-Carlton, Rancho Mirage. Mon-Thurs. 18 hrs. $450. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

February 24-28—**Diagnostic Imaging Update: Body Imaging, Mammography, MRI and Interventional.** Stanford University Medical Center at Ritz-Carlton Mauna Lani, Hawaii. Mon-Fri. 23.5 hrs. $550. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

February 27-30—**Advanced Seminars in Diagnostic Imaging.** UCSD at Ritz-Carlton, Laguna Niguel. Thurs-Sun. 20 hrs. $500. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

March 2-6—**Magnetic Resonance Imaging.** UCSD at Hotel del Coronado, San Diego. Mon-Fri. 27.25 hrs. $540. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

March 11-13—**12th Annual Current Approaches to Radiation Oncology, Biology, and Physics.** UCSF at Hotel Nikko, San Francisco. Wed-Fri. 18 hrs. $325. Contact: UCSF.

(Continued on Page 680)

CALL FOR ABSTRACTS

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Indications and Usage: *1) Short-term treatment of active duodenal ulcer, (2) maintenance therapy for duodenal ulcer patients at reduced dosage after healing of active ulcer, (3) short-term treatment of active benign gastric ulcer, (4) erosive gastroesophageal reflux disease, (5) treatment of pathological hypersecretory conditions*

Contraindications: *Tagamet is contraindicated for patients known to have hypersensitivity to the product*

Precautions: *Rare instances of cardiac arrhythmias and hypotension have been reported following the rapid administration of Tagamet (brand of cimetidine hydrochloride) Injection by intravenous bolus*

Symptomatic response to Tagamet therapy does not preclude the presence of a gastric malignancy There have been rare reports of transient healing of gastric ulcers despite subsequently documented malignancy

Reversible confusional states have been observed on occasion, predominantly in severely ill patients.

Tagamet has been reported to reduce the hepatic metabolism of warfarin-type anticoagulants, phenytoin, propranolol, chlordiazepoxide, diazepam, certain tricyclic antidepressants, lidocaine, theophylline and metronidazole Clinically significant effects have been reported with the warfarin anticoagulants, therefore, close monitoring of prothrombin time is recommended, and adjustment of the anticoagulant dose may be necessary when Tagamet is administered concomitantly Interaction with phenytoin, lidocaine and theophylline has also been reported to produce adverse clinical effects

However, a crossover study in healthy subjects receiving either Tagamet 300 mg q i.d or 800 mg h s. concomitantly with a 300 mg b i.d. dosage of theophylline (Theo-Dur®, Key Pharmaceuticals, Inc.) demonstrated less alteration in steady-state theophylline peak serum levels with the 800 mg h.s. regimen, particularly in subjects aged 54 years and older Data beyond ten days are not available (Note. All patients receiving theophylline should be monitored appropriately, regardless of concomitant drug therapy)

In a 24-month toxicity study in rats, at dose levels approximately 8 to 48 times the recommended human dose, benign Leydig cell tumors were seen These were common in both the treated and control groups, and the incidence became significantly higher only in the aged rats receiving Tagamet.

A weak antiandrogenic effect has been demonstrated in animals. In human studies, Tagamet has been shown to have no effect on spermatogenesis, sperm count, motility, morphology or in vitro fertilizing capacity

Pregnancy Category B Reproduction studies have been performed in rats, rabbits and mice at doses up to 40 times the normal human dose and have revealed no evidence of impaired fertility or harm to the fetus due to Tagamet. There are, however, no adequate and well-controlled studies in pregnant women Because animal reproductive studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed

Lack of experience to date precludes recommending Tagamet for use in children under 16 unless anticipated benefits outweigh potential risks; generally, nursing should not be undertaken by patients taking the drug since cimetidine is secreted in human milk

Adverse Reactions: *Diarrhea, dizziness, somnolence, headache. Reversible confusional states (e.g., mental confusion, agitation, psychosis, depression, anxiety, hallucinations, disorientation), predominantly in severely ill patients, have been reported Reversible impotence in patients with pathological hypersecretory disorders receiving Tagamet, particularly in high doses for at least 12 months, has been reported. The incidence of impotence in large-scale surveillance studies at regular doses has not exceeded that commonly reported in the general population Gynecomastia has been reported in patients treated for one month or longer Decreased white blood cell counts in Tagamet-treated patients (approximately 1 per 100,000 patients), including agranulocytosis (approximately 3 per million patients), have been reported, including a few reports of recurrence on rechallenge Most of these reports were in patients who had serious concomitant illnesses and received drugs and/or treatment known to produce neutropenia Thrombocytopenia (approximately 3 per million patients) and, very rarely, cases of aplastic anemia have also been reported Dose-related increases in serum transaminase have been reported Reversible adverse hepatic effects, cholestatic or mixed cholestatic-hepatocellular in nature, have been reported rarely Because of the predominance of cholestatic features, severe parenchymal injury is considered highly unlikely A single case of biopsy-proven periportal hepatic fibrosis in a patient receiving Tagamet has been reported Small, possibly dose-related increases in plasma creatinine have been reported Rare cases of fever, interstitial nephritis, urinary retention, pancreatitis and allergic reactions, including anaphylaxis and hypersensitivity vasculitis, have been reported. Rare cases of bradycardia, tachycardia and A-V heart block have been reported with H_2-receptor antagonists. Reversible arthralgia, myalgia and exacerbation of joint symptoms in patients with preexisting arthritis have been reported rarely Rare cases of polymyositis have been reported, but no causal relationship has been established Mild rash and, very rarely, cases of severe generalized skin reactions (e.g., Stevens-Johnson syndrome, epidermal necrolysis, erythema multiforme, exfoliative dermatitis and generalized exfoliative erythroderma) have been reported with H_2-receptor antagonists. Reversible alopecia has been reported very rarely*

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Biomedical Science

Jejunal Brush-Border Folate Hydrolase
A Novel Enzyme

CHARLES H. HALSTED, MD, *Davis, California*

Presented at the annual meeting of the Western Association of Physicians, Carmel, California, February 6-7, 1991.

Dietary folate, a vitamin required for DNA synthesis and cell regeneration, occurs as pteroylpolyglutamates that are hydrolyzed to pteroylglutamate during the process of intestinal absorption. Studies from our laboratory over the past 15 years have shown that jejunal brush-border folate hydrolase is essential and rate-limiting in folate absorption. Brush-border folate hydrolase activity and pteroylpolyglutamate hydrolysis are inhibited in diseases and conditions associated with folate deficiency, including celiac and tropical sprue, the use of sulfasalazine to treat inflammatory bowel disease, and chronic alcoholism. Brush-border folate hydrolase is an exopeptidase located on the jejunal brush-border surface that liberates hydrolytic products of pteroylpolyglutamates in a progressive fashion, with a final release of pteroylglutamate. Subsequent steps in folate absorption include uptake by a brush-border folate-binding-protein receptor and transport across the brush-border membrane into the enterocyte. These steps are probably followed by an intracellular synthesis of pteroylglutamates for folate-dependent reactions and intracellular hydrolysis to pteroylglutamate for transport across the basolateral membrane to the portal circulation. In pigs, the active form of jejunal brush-border folate hydrolase has a molecular weight of 240 kd and is probably a homodimer of the 120-kd protein found after immunoprecipitation with specific antibody. Regulating the synthesis and expression of brush-border folate hydrolase may be critical to the availability of dietary folate.

(Halsted CH: Jejunal brush-border folate hydrolase—A novel enzyme. West J Med 1991 Dec; 155:605-609)

Folate is a water-soluble vitamin found mainly in foliage or animal products. The adult daily requirement for folate is 3 μg per kg of body weight, with a minimal daily requirement of 50 μg and a storage capacity sufficient for about 150 days in a healthy adult.[1] The principal folate-dependent reactions involve amino acid interconversions and nucleic acid synthesis. Of greatest functional significance is the folate-vitamin B_{12} interaction, in which circulating 5-methyltetrahydrofolate is demethylated to tetrahydrofolate during the conversion of homocysteine to methionine. This reaction is followed by the production of 5,10-methylenetetrahydrofolate, the essential cofactor for thymidylate synthetase in the conversion of deoxyuracil to deoxythymidine in the synthesis of DNA. As a result of this interaction in folate metabolism, a deficiency of either vitamin B_{12} or folate leads to a paucity of DNA expression in rapidly regenerating tissues, such as the bone marrow and the intestinal epithelium.

Clinically, the bone marrow lesion presents as megaloblastic anemia, whereas the intestinal lesion of folate deficiency causes diarrhea and malabsorption of water-soluble nutrients.[2] Underscoring the importance of the absorptive process in regulating the folate status, folate deficiency is commonly associated with intestinal malabsorption syndromes such as celiac and tropical sprue. In addition, folate absorption is impaired in chronic alcoholism and during the long-term use of sulfasalazine (previously called salicylazosulfapyridine) and phenytoin.[3]

Folate Absorption From the Human Jejunum

The folate molecule consists of pteroic acid and glutamate, that is, pteroylglutamate (PteGlu), which is attached to as many as six additional glutamates in γ-peptide linkage (Figure 1). The pteroylpolyglutamate form ($PteGlu_n$) predominates in the diet and within cells, where it enters into folate-dependent reactions. The monoglutamyl form is required for the transport of folate across cell membranes. The uptake of dietary $PteGlu_n$ by intestinal epithelial cells requires two steps: hydrolysis of the glutamate side chain and membrane transport of the PteGlu derivative into the cells.

We initially studied the intestinal uptake of folate using the technique of triple-lumen tube jejunal perfusion in normal human volunteers. Separately labeled folates, PteGlu labeled with tritium and $PteGlu_7$ labeled with radioactive carbon, were infused in equimolar concentrations into the proximal jejunum of fasting subjects. By analyzing specimens aspirated through the tube from sites downstream from the infusion port, we measured the intestinal uptake of each labeled folate and the simultaneous appearance of hydrolytic products of ^{14}C-$PteGlu_7$ in the luminal contents.[4,5]

ABBREVIATIONS USED IN TEXT

BBFH = brush-border folate hydrolase
ICFH = intracellular folate hydrolase
PteGlu = pteroylglutamate
$PteGlu_n$ = pteroylpolyglutamate

From the Division of Clinical Nutrition and Metabolism, Department of Internal Medicine, University of California, Davis, School of Medicine.

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Reprint requests to Charles H. Halsted, MD, Division of Clinical Nutrition and Metabolism, TB 156, University of California, Davis, School of Medicine, Davis, CA 95616.

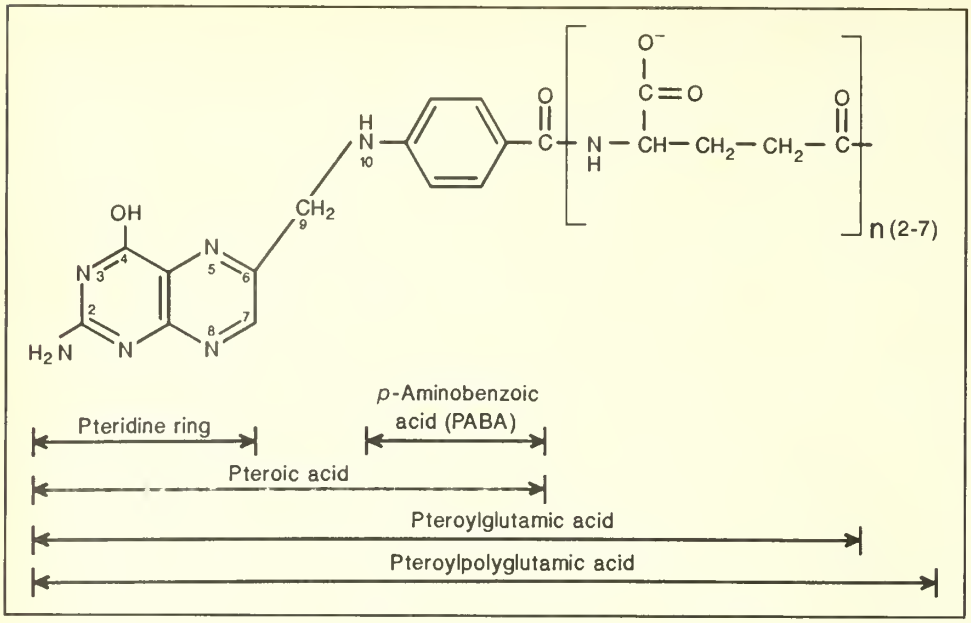

Figure 1.—The chemical structure of folate, or pteroylpolyglutamic acid ($PteGlu_n$), is shown. A side chain of glutamate molecules is bound in γ-peptide linkage to pteroylglutamate (PteGlu). Substitutions, such as methyl and formyl groups, and reductions occur in the pteridine ring. Dietary folate predominantes as $PteGlu_n$, whereas metabolic reactions use substituted and reduced $PteGlu_n$. Folate circulates as 5-methyltetrahydro-PteGlu.

In normal subjects[5,6] and in patients with various clinical conditions,[5,7,8] the uptake of perfused ^{3}H-PteGlu from the human jejunum exceeded that of ^{14}C-$PteGlu_7$ by about 150% (Figure 2). Neither aging nor ulcerative colitis affected the jejunal uptake of either folate.[6,8] Two diseases of the intestinal mucosa, however—celiac and tropical sprue—profoundly decreased the jejunal uptake of each folate.[5,7] Appropriate treatment of each mucosal disease increased the uptake of each folate. In normal subjects and in each clinical condition, the slower uptake of the conjugated ^{14}C-$PteGlu_7$ suggested that folate hydrolysis is the rate-limiting factor in the overall process of folate absorption.

More detailed evaluation of the hydrolytic process was afforded by a chromatographic separation of products of ^{14}C-$PteGlu_7$ that appeared in downstream aspirates during folate perfusion (Figure 3-A).[4,5] The disappearance of ^{14}C-$PteGlu_7$ was complex and involved the progressive appearance of intermediate chain-length folates followed by end-product ^{14}C-PteGlu.[4] We interpreted this process as a progressive hydrolytic reaction that preceded the jejunal uptake of the end product. In vitro experiments indicated that luminal contents alone could not generate hydrolytic products, whereas homogenates of human jejunal mucosa released all possible hydrolytic products after incubation with ^{14}C-$PteGlu_7$ (Figure 3-B). These experiments suggested that the hydrolytic reaction observed during the jejunal perfusion of ^{14}C-$PteGlu_7$ occurred on the surface membrane or within the epithelial cells.

Jejunal Folate Hydrolases—Biochemical and Clinical Studies

To identify and characterize human intestinal folate hydrolase, we measured enzyme activity in separated brush-border membranes and soluble intracellular fractions of jejunal mucosa. These and subsequent experiments used Pte-$(Glu)_2$-(^{14}C)-Glu, a synthetic radiolabeled substrate,[9] and mucosa obtained from the jejunum of patients undergoing elective surgical therapy for morbid obesity. We initially discovered a brush-border folate hydrolase (BBFH) with a pH optimum of 6.5 that was distinct from an intracellular folate hydrolase (ICFH) with a pH optimum of 4.5 and that had a different response to enzyme inhibitors.[10] We then purified human jejunal BBFH and showed that it is an exopeptidase that liberates the hydrolytic products of $PteGlu_n$ (Figure 4)[11] in the same progressive stepwise way as seen during human jejunal perfusion (Figure 3-A).[4] Furthermore, we showed that the intermediate chain-length hydrolytic products are competitive inhibitors, each with equal affinity for BBFH, thus limiting the rate of the overall sequence of reactions.[11] In contrast, we found that partially purified human ICFH is an endopeptidase that liberates PteGlu as an initial hydrolytic product,[12] inconsistent with the hydrolytic sequence observed during perfusion studies.

Brush-border folate hydrolase activity in jejunal biopsy

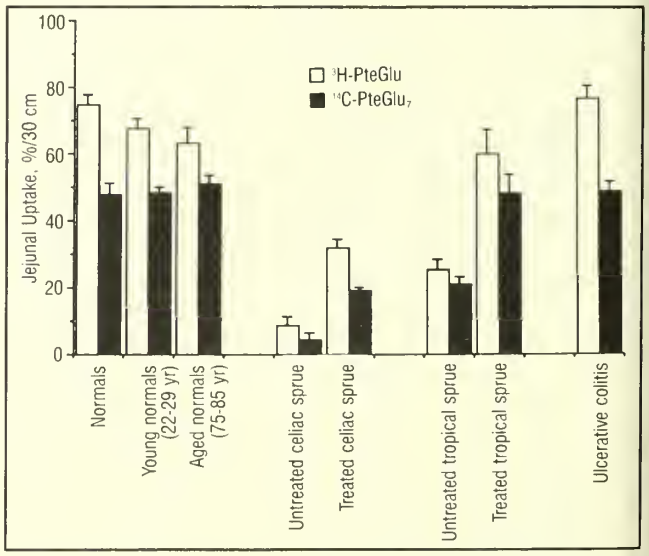

Figure 2.—The results of jejunal perfusion studies are given for normal subjects of different ages and for patients with untreated and treated celiac and tropical sprue and with ulcerative colitis in the absence of treatment with sulfasalazine. In each condition, the uptake of perfused pteroylglutamate (PteGlu) labeled with tritium exceeded that of pteroylpolyglutamate ($PteGlu_7$) labeled with carbon 14 ($P<.05$), suggesting that the intestinal absorption of $PteGlu_n$ is limited by the requirement of its hydrolysis to PteGlu. The jejunal uptake of each folate was improved by the appropriate treatment of celiac or tropical sprue (from Halsted et al,[5] Bailey et al,[6] Corcino et al,[7] and Halsted et al[8]).

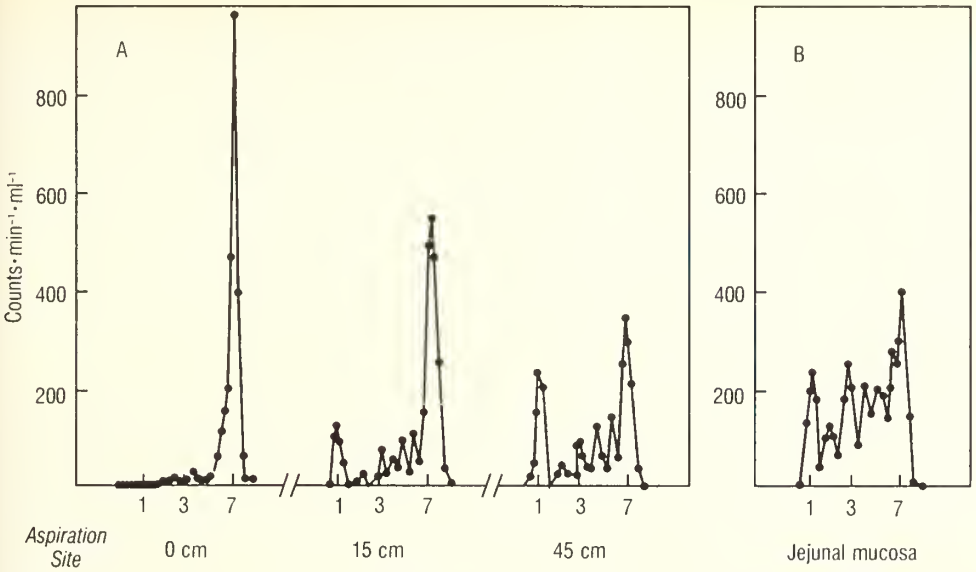

Figure 3.—Chromatographic patterns of hydrolytic products of pteroylpolyglutamate labeled with carbon 14 (^{14}C-PteGlu$_7$) are shown during human jejunal perfusion **(A)** and after 15 minutes of incubation with a homogenate of normal human jejunal mucosa **(B)**. As shown **(A)**, during jejunal perfusion, the labeled folate (infusion site, 0 cm) was hydrolyzed in progressive fashion, releasing all possible intermediates and final product pteroylglutamate labeled with carbon 14 to the lumen (aspiration sites 15 and 45 cm from the infusion port). An identical pattern of hydrolytic products was obtained by in vitro incubation of ^{14}C-PteGlu$_7$ with a homogenate of normal human jejunal mucosa **(B)**, whereas no hydrolysis resulted from incubation with intestinal juice obtained during saline perfusion (not shown). These studies suggested that folate hydrolysis occurs on the surface of the jejunal mucosa (from Halsted et al[4] and Halsted et al[5]).

specimens was substantially decreased in patients with untreated celiac sprue but was adaptively increased in the jejunum of patients with previous resections of the distal small intestine; by contrast, ICFH activity was unaffected by intestinal diseases.[13] In a jejunal perfusion study of patients with ulcerative colitis, we found that adding the anti-inflammatory drug sulfasalazine to the perfusion solution caused a dose-related inhibition of PteGlu$_7$ hydrolysis,[8] consistent with the finding that sulfasalazine competitively inhibits isolated BBFH.[14]

Jejunal Transport of Pteroylglutamate

Following the hydrolysis of PteGlu$_n$ by BBFH, end-product PteGlu is transported across the brush-border membrane by an active, saturable, and pH-dependent process.[15] Recent studies using isolated nonintestinal cell systems have shown that PteGlu is initially bound to a glycophospholipid-linked folate-binding–protein receptor on the cell membrane. The vitamin-receptor complex is internalized and then transferred to an anion carrier for transport into the cell.[16] In this model, the concentration gradient for folate uptake is maintained by the intracellular synthesis of transported PteGlu to PteGlu$_n$,[16,17] the intracellular form of folate that best serves the metabolic needs of the cell.[17] Because folate circulates exclusively in the monoglutamyl form, it is likely, though unproven, that ICFH is required to convert intracellular PteGlu$_n$ back to PteGlu before transport across the basolateral membrane to the portal circulation.

Although folate-binding protein has been identified in placenta, kidney, choroid plexus, and several isolated cell systems,[18] its existence in the intestine and its potential role in folate uptake have been controversial. Recently Reisenauer used affinity labeling with PteGlu to show a 56-kd binding protein in pig jejunal brush-border membranes.[19] Others have cloned folate-binding protein from a complementary DNA library of isolated human colon cancer cells and shown that its deduced amino acid sequence is consistent with glycophospholipid anchoring to the cell membrane.[20]

To demonstrate that the hydrolysis of PteGlu$_n$ and the binding of PteGlu are functions of separate intestinal proteins, we compared the kinetics of each process in isolated pig jejunal brush-border vesicles.[21] The affinity of the membranes for binding PteGlu, K_d 80 nmol per liter, was much greater than the affinity for the hydrolysis of PteGlu$_3$, K_m 1.7 μmol per liter, whereas the respective substrate for each func-

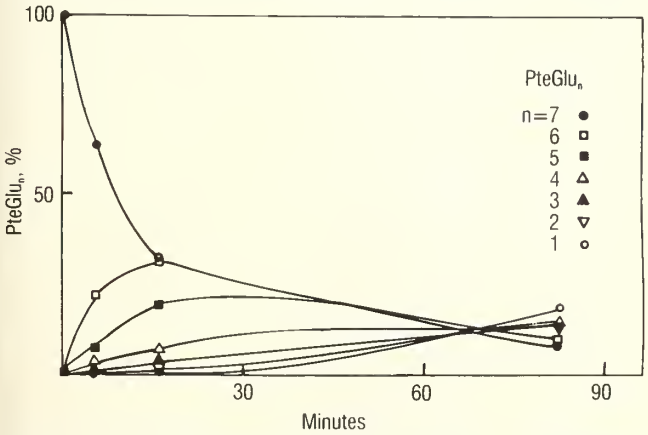

Figure 4.—Rates of disappearance of 22 μmol per liter of pteroylpolyglutamate (PteGlu$_7$) and the timed appearance of its hydrolytic products are shown during in vitro incubation with brush-border folate hydrolase. Products were identified after timed incubations by high-performance liquid chromatography. Data show an exopeptidase reaction that liberated various intermediate PteGlu$_n$ before end-product pteroylglutamate (from Chandler et al[11]).

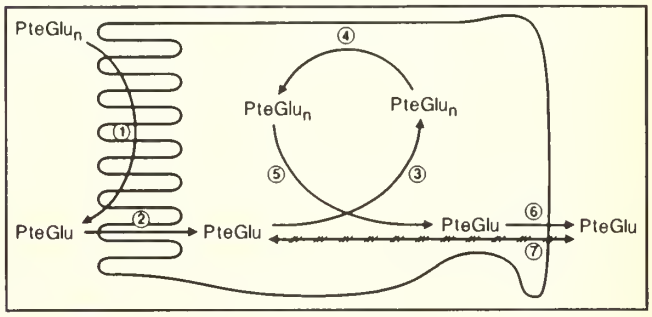

Figure 5.—Hypothetic scheme is given for hydrolysis and transport of folate across enterocytes. Reactions include ① hydrolysis of pteroylpolyglutamate (PteGlu$_n$) by brush-border folate hydrolase, ② binding by folate-binding protein and transport of pteroylglutamate (PteGlu) across the brush-border membrane, ③ synthesis of intracellular PteGlu$_n$ by folate synthetase, ④ intracellular folate reactions using PteGlu$_n$, ⑤ hydrolysis of intracellular PteGlu$_n$ by intracellular folate hydrolase, ⑥ transport of PteGlu across the basolateral membrane to villous capillaries, and ⑦ presumed bidirectional transport of PteGlu between circulation and enterocyte.

tion was a weak competitive inhibitor of the opposite function.[21] These studies suggest that different but related brush-border membrane proteins are required for the hydrolysis of $PteGlu_n$ and the binding of PteGlu.

Figure 5 depicts my hypothesis for the complex sequence of steps in the absorption of dietary folate by the jejunal epithelial cell, or enterocyte, including the separate roles for BBFH, folate-binding protein, and ICFH.

An Animal Model for Folate Absorption

Seeking an animal model for folate absorption, we observed that BBFH was present in the jejunal mucosa of pigs but was absent from laboratory rats and monkeys, which expressed only ICFH.[22] Elsenhans and co-workers described rat ICFH as an endopeptidase with characteristics similar to those we found for human ICFH.[22,23] We do not know why BBFH is absent in some species. The lack of enzyme induction by its dietary substrate $PteGlu_n$ might provide an explanation because laboratory chow for rats and monkeys contains monoglutamyl folate.

Our laboratory and others showed similar characteristics of pig and human jejunal BBFH.[11,24,25] Each enzyme is an exopeptidase with a pH optimum of 6.5 and a K_m in the range of 0.6 to 1.0 μmol per liter. According to the gel filtration method, which separates proteins on the basis of both size and shape, both pig and human BBFH are large molecules.[11,24] Using polyacrylamide gel electrophoresis of native proteins, Gregory and associates showed that pig BBFH has a molecular weight of 240 kd.[25] An additional folate hydrolase has recently been identified in pig pancreatic secretions.[26] This endopeptidase probably plays a minor role in folate digestion because its stimulated capacity for hydrolyzing $PteGlu_n$ is about 200-fold less than that of BBFH.[27]

We used pigs to show the functional specificity of BBFH in folate digestion.[27] First, the site of hydrolysis of $PteGlu_3$ was compared in vivo with the sites of activity of BBFH and ICFH. After solutions were incubated for five minutes in isolated intestinal segments of an anesthetized pig, $PteGlu_3$ was hydrolyzed to PteGlu in the jejunum but was unchanged in the ileum. Second, contrasting the activities of both mucosal folate hydrolases in equidistant segments along the intestine, we found that BBFH activity was maximal in the duodenum and proximal ileum but only minimal in the distal ileum, whereas ICFH activity was similar throughout the small intestine. Thus, the parallel of the location of BBFH activity with the jejunal site of in vivo hydrolysis of $PteGlu_3$ is consistent with clinical and biochemical evidence from the human studies described above that BBFH—not ICFH—plays a specific role in the initial digestion of dietary $PteGlu_n$.

Immunologic methods were used to confirm the jejunal location of BBFH and to define its molecular size.[27] Pig jejunal BBFH was purified to homogeneity and used to produce polyclonal and monoclonal antibodies in mice. Following incubation with a homogenate of pig jejunal mucosa, the polyclonal antibody immunoprecipitated BBFH but not ICFH, thereby showing its specificity for BBFH. Electrophoretic separation of the precipitated and denatured enzyme identified a protein band at 120 kd. An immunoprecipitate of identical size was obtained using the monoclonal antibody to BBFH. Immunohistochemistry using the monoclonal antibody and an enzyme-linked antimouse secondary antibody showed that BBFH is localized to the brush-border surface of the jejunum but not of the ileum, consistent with the distribution of its activity, as described earlier. Immunoblotting (Western blots) with polyclonal and monoclonal antibodies identified protein bands at 195 kd and 120 kd in the jejunum but no protein bands in the ileum (Figure 6). These studies showed the specificity of BBFH for folate digestion in pig jejunum and indicated that BBFH is a jejunal enzyme with two protein units. Thus, whereas immunoprecipitation identified the active enzyme at 120 kd, immunoblotting identified an additional and putative precursor protein at 195 kd. The 240-kd native protein shown by Gregory and colleagues[25] may represent a homodimer of the 120-kd denatured protein identified in our studies.[27]

Effects of Chronic Alcoholism on Folate Absorption

Previous clinical studies showed that the jejunal uptake of perfused ^{3}H-PteGlu was subnormal in folate-deficient alcohol-dependent persons who binge drink.[28,29] We used the pig model to study the effects of chronic alcoholism on the two stages of folate absorption, the hydrolysis of $PteGlu_n$ and the uptake of end-product PteGlu. Levels of liver folate were low in miniature pigs after a year of consuming diets containing 50% of calories as ethanol and all essential nutrients including adequate dietary folate.[30] Both in vivo and in vitro approaches were used to compare folate absorption in alcoholic and control pigs.

In vivo, we infused $PteGlu_3$ or PteGlu through tubes that had been surgically implanted in the jejunum. Pteroylglutamate$_3$ hydrolysis in an alcoholic pig was about 35% of that found in a control animal, whereas PteGlu uptake was similar in both animals.[30] Using in vitro preparations of jejunal

Figure 6.—Western blot results are shown of pig jejunal and ileal mucosa incubated with monoclonal antibody to purified brush-border folate hydrolase (BBFH) and secondary anti-pig antibody linked to alkaline phosphatase and stain. Data show two protein bands for BBFH: the active form of the enzyme at 120 kd and a putative precursor at 195 kd. Consistent with the distribution of enzyme activity (not shown), the protein is expressed in the jejunum and not in the ileum (reprinted from Chandler et al[27] with permission of the American Physiological Society).

brush-border membranes, we found a significant 50% inhibition of BBFH in the alcohol-fed group but no differences in PteGlu uptake.[31] Thus, one year of feeding alcohol to miniature pigs selectively inhibited BBFH and the hydrolysis of $PteGlu_3$ without affecting the uptake of end-product PteGlu. Because the decrease in BBFH activity was not accompanied by changes in microviscosity or the chemical composition of the brush-border membranes, the data suggest that long-term ethanol feeding inhibited the production of the BBFH protein, initiating the development of folate deficiency in alcoholism.

Future Studies

To study the molecular structure and regulation of BBFH, we have constructed a complementary DNA library of pig intestine to isolate an authentic clone of the gene for BBFH. This will enable us to study species homology between pig and human BBFH and to develop a specific nucleotide probe to study enzyme development and the effects of dietary factors, diseases, drugs, and intestinal adaptation on the synthesis and expression of BBFH. Because BBFH regulates the supply of dietary folates to the intestinal mucosa, learning about its regulation will increase the understanding of the pathogenesis of altered enterocyte proliferation and function in diseases and conditions causing folate malabsorption.

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Biomedical Science

Intravenous Immune Globulin Use in Patients With Human Immunodeficiency Virus-Related Thrombocytopenia Who Require Dental Extraction

MARK U. RARICK, MD; PAM BURIAN, PA-C; NELSON DE GUZMAN, PA-C; BYRON ESPINA; TERRI MONTGOMERY, RN; DENISE JAMIN, PharmD; *and* ALEXANDRA M. LEVINE, MD, *Los Angeles, California*

Five patients with human immunodeficiency virus (HIV)-related immune thrombocytopenia who were undergoing dental extraction were treated with intravenous immune globulin (IVIG). All patients received IVIG, 1 gram per kg, the day before the dental extraction and again the day of the dental extraction. Four patients had a previous history of minor clinical bleeding. The median baseline platelet count before extraction was 20×10^9 per liter (range 13 to 44). The median peak platelet count was 100×10^9 per liter (range 56 to 528) following infusion. This peak response was achieved by day 2 in 3 patients and by days 5 and 7 in 1 patient each. No patients had complications or toxicity from the infusions or perioperative bleeding. No patients required blood product transfusions for the surgical procedure. In conclusion, IVIG infusion should be considered in patients with HIV-related immune thrombocytopenia requiring surgical procedures when a prompt rise in platelet count is desired.

(Rarick MU, Burian P, de Guzman N, et al: Intravenous immune globulin use in patients with human immunodeficiency virus-related thrombocytopenia who require dental extraction. West J Med 1991 Dec; 155:610-612)

Infection by the human immunodeficiency virus (HIV) may result in unique opportunistic infections, neoplasms, and autoimmune disorders.[1,2] Immune-mediated HIV-related thrombocytopenia was described early in the HIV epidemic and is not unusual, occurring in as many as 11% of patients with HIV infection.[3-6]

Patients with HIV-related thrombocytopenia may present with a spectrum of bleeding abnormalities, including petechiae, ecchymoses, epistaxis, and gum bleeding. In rare instances, gastrointestinal or central nervous system hemorrhage may occur.[4,6] The cause of thrombocytopenia in this setting is multifactorial and includes immune-mediated peripheral destruction, splenic sequestration, decreased platelet production due to medications, and accompanying opportunistic infections and neoplasms.[7-10] The management of thrombocytopenia in patients with HIV infection must therefore be tailored to the individual circumstance, and patients' underlying immunodeficiency caused by HIV must be considered. Treatment options include corticosteroids (prednisone), splenectomy, zidovudine, intravenous immune globulin (IVIG), interferon alfa, danazol, and vincristine sulfate,[11-14(p204),15(p332),16-24] which have varying response rates and toxicities.

The management of patients with symptomatic thrombocytopenic bleeding or those undergoing surgical procedures has not been well described. Infusing IVIG has been shown to be effective in the short-term treatment of HIV-related immune thrombocytopenia.[25,26] At the Los Angeles County–University of Southern California Medical Center, we observe a large number of patients with immune thrombocytopenia in the HIV Comprehensive Treatment Clinic and therefore have observed prospectively a cohort of patients with HIV-related immune thrombocytopenia who required dental extractions. This article describes our experience with the use of IVIG in these patients to prevent perioperative bleeding complications.

Patients and Methods

Patient Population

Patients were included in the study if they had a diagnosis of immune-mediated HIV-related thrombocytopenia as defined by a platelet count of less than 50×10^9 per liter (50,000 per μl), which puts them at higher risk for bleeding during surgical procedures. Patients were staged in accordance with the Centers for Disease Control classification for HIV infection.[27] Patients with evidence of opportunistic infection or neoplasms diagnosed by bone marrow biopsy or aspiration were excluded from the study.

Treatment Regimen

All patients were treated with IVIG (Gamimune-N, pH 4.25; Cutter Biologic Corporation, West Haven, Connecticut). Each patient received 1 gram per kg intravenously at a rate not to exceed 0.04 ml per kg per minute, beginning the day before dental extraction. On the day of the dental extraction, a second infusion of IVIG, 1 gram per kg, was started that infused during the extraction procedure. The patients then returned to the HIV clinic to finish the immune globulin infusion.

Physical examinations were done before extraction and at one and two weeks after the extraction.

Laboratory Studies

Baseline studies included a leukocyte count, hemoglobin level, and granulocyte, platelet, and $CD4^+$ lymphocyte

From the Departments of Internal Medicine and Pharmacology, Section of Hematology, University of Southern California School of Medicine, Los Angeles.
Reprint requests to Mark U. Rarick, MD, USC School of Medicine, Norris Cancer Hospital, 1441 Eastlake Ave, Rm 162, Los Angeles, CA 90033.

ABBREVIATIONS USED IN TEXT

HIV = human immunodeficiency virus
IVIG = intravenous immune globulin

counts. Platelet counts were also measured on day 2 of the infusion and at one and two weeks after the IVIG infusion.

Results

Five men with sexually transmitted HIV infection were studied. None of the patients reported intravenous drug use or a previous blood product transfusion as risk factors for HIV infection. The median age of the group was 38 years (range 22 to 41 years). The median history of HIV-related thrombocytopenia was 13 months (range 1 to 15 months). Four patients had stage III HIV infection, and one patient had stage IVA manifested by unexplained low-grade fevers and weight loss. Four of the five patients had a history of bleeding that consisted of petechiae in three, traumatic ecchymoses in three, gum bleeding in three, and gastrointestinal bleeding in one. One patient had no history of bleeding but presented with a platelet count of 40×10^9 per liter before dental extraction.

Baseline physical examinations in three patients revealed lower extremity petechiae and scattered ecchymoses. All patients had generalized lymphadenopathy. The laboratory values are shown in Table 1. The median baseline platelet count before extraction was 20×10^9 per liter (range 13 to 44×10^9 per liter). The median baseline $CD4^+$ lymphocyte count was 340 per μl (range 59 to 449 per μl). The median leukocyte count was 4.6×10^9 per liter (4,600 per μl) (range 3.1 to 6.8×10^9 per liter), and the median hemoglobin value was 142 grams per liter (14.2 grams per dl) (range 141 to 151 grams per liter).

All five patients received the IVIG treatment for two days. The median dose of IVIG was 69 grams (range 50 to 80 grams). The number of teeth extracted varied: two patients had one, one patient had two, and two had three extractions.

As shown in Table 1, all five patients responded to IVIG treatment with a median peak platelet count of 91×10^9 per liter (range 56 to 528×10^9 per liter) after the infusion, which was achieved by day 2 in three patients, day 5 in one patient, and day 7 in one patient. The response was transient in four of the five patients with a median nadir platelet count of 26×10^9 per liter at a median follow-up of three weeks. There was no unusual bleeding during the extraction nor was there any observed toxicity from the IVIG infusion. On physical examinations one week and two weeks following dental extraction, no bleeding was seen from the sites of extraction. None of the patients required blood product support.

Discussion

Treatment strategies for patients with immune-related thrombocytopenia associated with HIV infection are varied.[11-24] Most of these reports emphasize long-term management. We have prospectively observed five patients with sexually transmitted HIV infection who underwent surgical procedures known to interfere with hemostatic plug formation. Further, although patients with HIV-related thrombocytopenia may not have clinical bleeding, it would be expected that persons undergoing dental extraction with platelet counts of less than 20×10^9 per liter would be at risk for such an occurrence.

In this study, all five patients had substantial platelet count increases immediately after the IVIG infusion. All were able to undergo the subsequent dental extractions without complications or significant bleeding, either during the procedure or within the following two weeks.

It is estimated that as many as 1.5 million people are infected with HIV in the United States.[28] Because immune thrombocytopenia in these patients is not uncommon, the development of strategies for therapy is important. As HIV infection has become a chronic condition with the use of antiretroviral therapy and prophylactic antibiotics to decrease the incidence of opportunistic infections, practicing physicians will need to manage common medical problems such as dental extraction. For those patients who have immune thrombocytopenia (in our experience $< 50 \times 10^9$ per liter) and who require operative procedures, a trial infusion of IVIG should be considered. The long-term control of the thrombocytopenia will require alternative measures, such as with zidovudine or possibly interferon alfa.

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TABLE 1.—*Laboratory Values for 5 Patients With HIV-Related Thrombocytopenia Before and After Dental Extraction*

Patient	Sex	Age, yrs	Previous Immune Thrombocytopenia, mos	Previous Treatment	HIV Stage	Baseline Platelet Count, $\times 10^9$/liter	Peak Platelet Count, $\times 10^9$/liter	Teeth Extracted	Complications
1	M	38	13	AZT, IVIG	III*	13	528	2	None
2	M	33	4	AZT, IVIG	III*	19	88	1	None
3	M	41	1	AZT, IVIG	III*	44	91	1	None
4	M	22	14	AZT	IVA†	40	56	3	None
5	M	39	15	AZT, IVIG	III*	20	100	3	None

AZT = zidovudine, HIV = human immunodeficiency virus, IVIG = intravenous immune globulin

*HIV stage III = persistent generalized lymphadenopathy.
†HIV stage IVA = constitutional symptoms.

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Articles

Screening for Hepatitis B During Pregnancy
Awareness of Current Recommendations Among Washington Hospitals

THOMAS R. ENG, VMD, MPH, *Washington, DC;* MARY L. BORGES *and* VIVIAN K. HARLIN, MD, MSPM, *Olympia; and* JOHN M. KOBAYASHI, MD, MPH, *Seattle, Washington*

Acute care hospitals in Washington State that reported births (n=77) were surveyed regarding their awareness of and compliance with the Centers for Disease Control recommendations for hepatitis B screening of pregnant women. Of these, 62 hospitals (81%) were aware of the recommendations and 39 (51%) routinely screened pregnant women who did not have a history of prenatal care at the time of delivery. In all, 68 hospitals (88%) had hepatitis B vaccine and 54 (70%) had hepatitis B immune globulin available on site. Despite awareness of the current recommendations for hepatitis B screening, barriers exist that prevent many hospitals from fully implementing them.

(Eng TR, Borges ML, Harlin VK, Kobayashi JM: Screening for hepatitis B during pregnancy—Awareness of current recommendations among Washington hospitals. West J Med 1991 Dec; 155:613-615)

Approximately 18,000 infants are born in the United States each year to women who test positive for hepatitis B surface antigen (HBsAg).[1] These infants are at high risk of becoming carriers of hepatitis B and for the development of primary hepatocellular carcinoma and chronic liver disease. Administering hepatitis B immune globulin (HBIG) and hepatitis B vaccine to these infants is highly effective in preventing the perinatal transmission of hepatitis B virus (HBV).[3,4]

In 1984, to identify infants born to HBsAg-positive women, the Centers for Disease Control (CDC) recommended prenatal HBsAg screening for women in certain high-risk groups.[5] Several studies later reported that this method of screening was ineffective in identifying many infants at risk and proposed that all pregnant women be screened for HBsAg as part of their prenatal care.[6-9]

In June 1988, CDC recommended prenatal HBsAg screening of all women or, for women who do not have a history of prenatal care, screening at the time of delivery.[10] Except for a report on follow-up vaccination of infants born to HBsAg-positive women at one hospital,[11] there is no published information on hospitals' awareness of or compliance with the current CDC recommendations. We report the results of a survey of acute care hospitals in Washington State regarding their awareness and implementation of the CDC recommendations for HBsAg screening of women a year after these recommendations were published.[10]

Methods

In July 1989, a questionnaire and a copy of the CDC recommendations for HBsAg screening of all pregnant women[10] were sent to the heads of obstetric services in the 77 acute care hospitals that reported births in Washington in 1989. The questionnaire requested self-reported information on awareness of and compliance with the CDC recommendations and the availability of hepatitis B vaccine at each hospital. Data on the availability of HBIG at these hospitals were collected as part of an annual telephone survey of hospital pharmacies.

Reported awareness of and compliance with the current CDC recommendations and the availability of hepatitis B vaccine and HBIG were compared among hospitals by various hospital characteristics, including location (urban versus rural), size, proportion of Medicaid patients, and rate of reported HBV infection in the respective counties. A rural hospital was defined as one located outside the boundaries of a metropolitan statistical area or inside such an area but 30 minutes or more from an urban area with a population of 10,000 or more. Hospital data for fiscal year 1989 were obtained from the Hospital Financial Database and the Commission Hospital Abstract Reporting System of the Washington State Department of Health. Statistical methods used were the χ^2 test and the Wilcoxon rank sum test.

Results

All 77 acute care hospitals in Washington that had reported births in 1989 responded to the survey. Of respon-

TABLE 1.—*Reported Awareness of the Centers for Disease Control's (CDC) Recommendations for Hepatitis B Surface Antigen Screening of All Pregnant Women by Selected Characteristics of 77 Hospitals in Washington State, 1989*

	Aware of CDC Recommendations?		
Hospital Characteristic	*Yes*	*No*	*P Value**
Urban location, n=39	32	7	.96†
Rural location, n=38	30	8	
Median No. of total admissions	3,333	2,572	.07
Median percentage of Medicaid patients	18	19	.60
Median rate (per 100,000 persons) of reported HBV in county	18	18	.90

HBV=hepatitis B virus

*Significance was determined using the Wilcoxon rank sum test unless indicated otherwise.

†Significance was determined using the χ^2 test.

From the Division of Field Services, Epidemiology Program Office, Centers for Disease Control, US Public Health Service, Atlanta, Georgia (Dr Eng); the Immunization Program, Washington State Department of Health, Olympia (Ms Borges and Dr Harlin); and the Communicable Disease Epidemiology Office, Washington State Department of Health, Seattle (Dr Kobayashi). Dr Eng is now with the Office of Medical Services, US Peace Corps, Washington, DC.

Reprint requests to Mary L. Borges, Immunization Program, Washington State Department of Health, Airindustrial Park, MS LP-19, Olympia, WA 98504.

ABBREVIATIONS USED IN TEXT

CDC = Centers for Disease Control
HBIG = hepatitis B immune globulin
HBsAg = hepatitis B surface antigen
HBV = hepatitis B virus

dents, 77% were nurses or nurse practitioners and 23% were physicians.

A total of 62 hospitals (81%) were aware of the CDC recommendations for HBsAg screening of all pregnant women. Hospitals that reported a familiarity with the recommendations had a higher median number of total admissions than hospitals that were not familiar with the recommendations, but this difference was not statistically significant (Table 1).

Routine screening of pregnant women who did not have a history of prenatal care at the time of delivery was reported by 39 hospitals (51%). Urban hospitals were more likely than rural hospitals to screen such women routinely (64% versus 37%, Table 2). In addition, hospitals that screened routinely had a significantly higher number of admissions and a lower proportion of Medicaid patients.

In all, 68 hospitals (88%) had hepatitis B vaccine and 54 (70%) had HBIG available on site. Except for one hospital, all hospitals that had HBIG available on site also had hepatitis B vaccine. Hospitals that had both hepatitis B vaccine and HBIG on site were significantly more likely to be in an urban rather than a rural area (82% versus 55%), to have a higher number of admissions, and to be located in counties with higher rates of reported HBV infection (Table 3).

Discussion

Our estimates of awareness and compliance with screening guidelines should be considered gross estimates because we did not objectively measure self-reported awareness of the recommendations or validate self-reported screening practices. Survey respondents may have overreported awareness or compliance with the recommendations because a copy of the CDC recommendations was included with the survey.

Although a relatively large proportion of hospitals was familiar with the CDC recommendations for screening of all pregnant women, only half of the hospitals reported that they routinely screen women at delivery who do not have a history of prenatal care. The prevalence of HBV infection among pregnant women with no history of prenatal care is unknown, but such women are likely at higher risk of HBV infection than women who have had prenatal care. A recent study reported that 9% of HBsAg-positive pregnant women did not have a history of prenatal care, as compared with 4% of HBsAg-negative pregnant women.[6]

Infants born to women who test positive for HBsAg at the time of delivery should receive hepatitis B vaccine and HBIG within 24 hours[1]; therefore, quick access to hepatitis B vaccine and HBIG is important. An on-site supply would reduce the time spent locating and obtaining these biologic agents. Keeping them on site in small hospitals may not be justifiable, however, if the prevalence of HBV is low and a dependable source is nearby. In the hospitals surveyed, the availability of hepatitis B vaccine and HBIG (88% and 70%, respectively) was higher than the percentage of hospitals that routinely screen women without a history of prenatal care at delivery (51%). This suggests that a lack of these agents is not the primary reason for noncompliance with the CDC recommendations.

Our data indicate that rural hospitals are less likely to screen pregnant women for hepatitis B, although in 1989, the median rate of reported HBV infection in rural areas was not significantly different from that in urban areas of Washington (21 and 17 cases per 100,000 persons, respectively; Wilcoxon rank sum, $P = .77$). In contrast, a study in Washington in 1982 reported a decreased risk of HBV infection among rural hospital employees compared with their urban counterparts.[12]

Our results indicate that most hospitals in Washington are aware of the current CDC recommendations to screen pregnant women for hepatitis B, but many are not fully implementing them. Operational research is needed regarding the barriers to implementing hepatitis B screening of all pregnant women, especially those without a history of prenatal care.

TABLE 2.—*Reported Compliance With the Centers for Disease Control's Recommendations for Hepatitis B Surface Antigen Screening of Pregnant Women Without a History of Prenatal Care by Selected Characteristics of 77 Hospitals in Washington State, 1989*

Hospital Characteristic	Pregnant Women Without a History of Prenatal Care Screened Routinely? Yes	No	P Value*
Urban location, n = 39	25	14	.03†
Rural location, n = 38	14	24	
Median No. of total admissions	5,365	1,273	.0004
Median percentage of Medicaid patients	15	21	.007
Median rate (per 100,000 persons) of reported HBV in county	19	18	.38

HBV = hepatitis B virus

*Significance was determined using the Wilcoxon rank sum test unless indicated otherwise.
†Significance was determined using the χ^2 test.

TABLE 3.—*Availability of Hepatitis B Vaccine and Hepatitis B Immune Globulin (HBIG) by Selected Hospital Characteristics of 77 Hospitals in Washington State, 1989*

Hospital Characteristic	Hepatitis B Vaccine and HBIG Available on Site? Yes	No	P Value*
Urban location, n = 39	32	7	.02†
Rural location, n = 38	21	17	
Median No. of total admissions	4,715	1,267	.0006
Median percentage of Medicaid patients	18	19	.28
Median rate (per 100,000 persons) of HBV reported in county	20	17	.01

HBV = hepatitis B virus

*Significance was determined using the Wilcoxon rank sum test unless indicated otherwise.
†Significance was determined using the χ^2 test.

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EAR

A squirrel cracks walnuts on the roof,
crickets sing in the swamp,
zinnias in a blue vase sigh.
I lie flat, chin on my chest,
hands forgotten, feet under a blanket,
no phone calls, no doorbells, no TV,
no jewelry knocking against my body,
no squeaky clothes,
no one to call me daughter,
sister,
mother,
or wife.

Call me baby,
soft flower,
or ear.

Let me hear
the silence
that says what I want to say.

Let me rise from a civil grave
and speak one true word to my children
in this deafening age.

FREYA MANFRED
Bloomington, Minnesota

Articles

Charges for Comprehensive Obstetric Care at Teaching and Nonteaching Hospitals

A Comparison

GILAD S. GORDON, MD, MBA; STEPHAN E. SEFCIK, CPA, PhD; *and* JAMES P. LO GERFO, MD, MPH; *Seattle, Washington*

We compared total charges for obstetric care at a major teaching hospital and faculty group practice with those at 3 nonteaching centers in western Washington. The patients were all enrollees of an employee-based health maintenance organization. Charges were used as a proxy for costs and included all outpatient, inpatient, and physician charges. In the teaching system, patients were cared for by faculty and house staff; in the nonteaching settings, they received care from private physicians. No significant differences in total charges were found between the teaching and the nonteaching settings for all deliveries ($4,652 [N=90] versus $4,530 [N=335], $P>.5$). In the teaching setting, vaginal deliveries were slightly more expensive ($4,178 [n=75] versus $3,768 [n=250], $P=.15$), as were cesarean deliveries ($7,024 [n=15] versus $6,771 [n=85], $P>.5$). The rate of cesarean deliveries was lower in the teaching setting (17% versus 25%, $P=.10$), partially accounting for the similarity in total charges. The length of stay was similar in the teaching hospital (3.29 versus 3.14 days, $P>.5$). We conclude that the academic medical center as a total system of care can provide obstetric care as cost-effectively as nonteaching systems under the constraints of prepaid care.

(Gordon GS, Sefcik SE, LoGerfo JP: Charges for comprehensive obstetric care at teaching and nonteaching hospitals—A comparison. West J Med 1991 Dec; 155:616-620)

In recent years, there has been rising concern over the costs of medical care, especially in teaching hospitals. This concern has been heightened by recent trends toward capitation and price competition that threaten the financial viability of academic medical centers. Although previous studies have addressed the costs of inpatient hospital and physician services, there are few studies on the competitiveness of academic medical centers as comprehensive systems of care that include all costs of outpatient and inpatient care.

A number of studies have shown that inpatient care in teaching hospitals is more expensive than that at nonteaching hospitals, but these studies did not include the substantial cost components of outpatient and physician charges. Most of these studies were done before the diagnosis-related-groups (DRGs) era and, after corrections for case mix, estimated that teaching hospitals were 11% to 33% more expensive than nonteaching hospitals.[1-14] Although the reasons for the higher costs in the teaching hospital have never been fully ascertained, they have generally been attributed to incomplete correction for severity of illness or the additional costs of teaching.

To undertake a comprehensive study of the total costs associated with providing care, it is imperative to analyze *all* costs for a given medical condition. Furthermore, it is preferable to study a medical condition that is time-limited, has a definite end result, has sizable inpatient and outpatient components, and has varying methods of treatment. The care of obstetric patients is ideal because it meets all of these requirements. The variations in treatment are shown by the wide range in the frequency of cesarean deliveries within the United States and internationally, which reflects the partially elective nature of this procedure.[15-21] Hence, any analysis of charges for obstetric care must account for the variation in the rates of cesarean deliveries between different health care settings.

To evaluate if an academic medical center can perform as a competitive system of care, it is important to examine data on patients who are similar in their case complexity and are treated in similar geographic regions. We accomplished this by studying the costs of prenatal and obstetric care provided patients enrolled in one employee-based, group-network, managed-care system who were cared for by one of four multispecialty groups in western Washington.

Patients and Methods

Setting Description

The patients were all enrolled in Health Plus, a Blue Cross-sponsored health plan in Washington State that is a group-network managed-care system and a federally qualified health maintenance organization (HMO). The plan was founded in 1981 and has about 60,000 enrollees. Membership is restricted to employees or their families who are enrolled through group plans. The plan contracts with multispecialty physician group practices in Washington. Capitation fees are paid for each enrollee with stop-loss provisions for catastrophic high-cost cases. Patients select a physician group and choose a primary physician who serves as a gatekeeper for all referred care. Physicians submit bills as for fee-for-service patients, but the physician group practice is at risk for charges that exceed total capitation payments attributable to its enrolled patients.

We studied the charges for prenatal and obstetric care in

From the Department of Medicine, School of Medicine (Drs Gordon and LoGerfo), and the School of Business Administration (Dr Sefcik), University of Washington, Seattle.

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Reprint requests to Gilad S. Gordon, MD, MBA, Health Services Research Director, Synergen, 1885 33rd St, Boulder, CO 80301.

ABBREVIATIONS USED IN TEXT

DRG = diagnosis-related group
HMO = health maintenance organization

the four largest multispecialty clinics in western Washington that contract with the health plan. These included the university-based group practice and three other private multispecialty clinics within 30 miles of the teaching setting. In the teaching system, patients received prenatal care in hospital outpatient clinics and were admitted to the teaching hospital in which house staff participated in the care of all patients. Physicians at the three private clinics admitted their patients to one or two private hospitals per clinic, and the primary physicians (obstetricians or family physicians) cared for patients with no house-staff involvement.

Most of the care provided in all four settings is on a fee-for-service basis, but all practices also participate in various managed-care plans. All four settings are located in a similar geographic region and have similar costs for labor and for living expenses.

Patients

The study patients included all women in the health plan who were delivered of a child during the 24-month period from January 1, 1986, to December 31, 1987. To capture all relevant obstetric charges, outpatient data were analyzed starting March 1, 1985. The study analyzed the charges associated with pregnancy and delivery but not those associated with the care of the infant. To ensure comparability across groups, patients were included if they met the following criteria:

- Financial data existed for outpatient, physician, and inpatient charges;
- The patient was seen as an outpatient for at least two months;
- The outpatient and physician charges included at least one visit to a physician;
- The inpatient charges included at least a half day of an inpatient bed.

Data Description

Data were provided by the health plan from computerized billing records. These records reflect the charges submitted by physicians and hospitals, as if the patients were enrolled in a fee-for-service insurance plan, although the physicians and hospitals were actually paid on a prearranged capitated basis. The health plan requires this billing system so that it can know how its reimbursement schedule compares with fee-for-service arrangements. Hence, the charge and reimbursement data are recorded separately, and only the charge records were analyzed for this study. The inpatient data reflect all data related to inpatient services, including anesthesia charges. The outpatient and physician data reflect all outpatient charges, including primary care provider and consultation charges.

In the state of Washington, it is illegal for hospital charges to exceed costs by more than 5%. It is also illegal to cross-subsidize between hospital departments. Fortunately, the same accounting firm prepares the cost reports for all of the hospitals studied. Therefore, inpatient charges can serve as a reasonable proxy for costs, and any aggregate differences between inpatient charges and costs would be expected to be similar in all of the hospitals.

Birth certificate data were analyzed to verify the similarity of the two groups and to control for birth outcomes. These data were obtained from the state's vital records after appropriate human subjects committee approval was received.

Results

Overall, 425 of the 493 births (86%) that occurred between January 1, 1986, and December 31, 1987, met the inclusion criteria. There were no substantive differences in the exclusion rates among the settings. Table 1 shows the distribution of the patients according to teaching and nonteaching settings and the total charges. Notably, in the teaching setting, 17% of the deliveries were by cesarean section, whereas in the nonteaching setting 25% of the deliveries were by cesarean section ($P = .1$ by χ^2 analysis). As shown in Table 1, during the period of study, 90 patients in the teaching setting who were covered by the health plan were delivered of their infants at an average charge per patient of $4,652, and 335 patients in the nonteaching settings who were covered by the health plan had delivery at an average charge per patient of $4,530. This difference of $122 (2.7%) per patient was not statistically significant, with a 95% confidence interval of –$467 to $711.

The teaching hospital had higher charges per patient for both types of deliveries, but the differences were not significant. When the total charges were divided into outpatient and physician charges and inpatient charges, the outpatient and physician charges were similar. Inpatient charges reflected a

TABLE 1.—*Distribution of Patients by Setting and Total Prenatal and Obstetric Charges by Method of Delivery**

Setting	*Patients, No.*	*Average Total Charges ± SD, $*	*% Difference†*	*Average Outpatient/MD Charges ± SD, $*	*% Difference†*	*Average Inpatient Charges ± SD, $*	*% Difference†*
Teaching							
All patients	90	4,652 ± 2,578	+2.7	2,022 ± 835	+1.5	2,630 ± 2,158	+3.6
Vaginal deliveries	75	4,178 ± 2,495	+10.9	1,855 ± 773	+4.8	2,323 ± 2,198	+16.3
Cesarean deliveries	15	7,024 ± 1,454	+3.7	2,857 ± 618	+8.1	4,167 ± 1,056	+1.0
Nonteaching							
All patients	335	4,530 ± 2,224		1,992 ± 821		2,538 ± 1,881	
Vaginal deliveries	250	3,768 ± 1,445		1,770 ± 583		1,998 ± 1,241	
Cesarean deliveries	85	6,771 ± 2,581		2,644 ± 1,047		4,127 ± 2,465	

SD = standard deviation

*None of the differences between teaching and nonteaching settings are statistically significant.
†(Teaching charges – nonteaching charges)/nonteaching charges.

TABLE 2.—*Comparison of Settings Length of Stay, January 1, 1986, to December 31, 1987*

Delivery Method	Teaching Days	Teaching Patients, No.	Nonteaching Days	Nonteaching Patients, No.	P Value*
Vaginal	2.99	75	2.58	250	.04
Cesarean	4.77	15	4.79	85	>.50
Total	3.29	90	3.14	335	>.50

*Student's *t*-test analysis.

nonsignificant higher charge at the teaching hospital. As noted in Table 1, the findings for cesarean deliveries were similar.

Average charges per patient for total obstetric care in the three nonteaching settings were $4,391 (n = 179) for clinic 1, $4,601 (n = 84) for clinic 2, and $4,791 (n = 72) for clinic 3. The teaching setting, with an average charge per patient of $4,652 (n = 90), was neither the least nor the most expensive.

We also analyzed the length of hospital stay, the single most important determinant of hospital costs (Table 2). Considering all deliveries, the differences in the length of stay were minimal and not statistically significant.

Because no significant differences in charges for hospital days were found across settings, we undertook an analysis of individual patients' clinical characteristics to rule out the remote possibility that the nonteaching settings cared for "sicker" patients and that this was missed because of our assumption of comparable case mixes based on the plan data. We analyzed data from the comprehensive birth certificate registry in the state of Washington. Access was obtained to birth certificates for 286 of the 425 deliveries. This sample represented substantially all 1987 birth certificates (93.9% of teaching setting births and 93.6% of nonteaching setting births). For 1986, we analyzed only the birth certificates for which the father's first name could be identified (91.2% of teaching setting births and 21.6% of nonteaching setting births). Birth certificates from years other than 1987 could not be retrieved without this identifier. These birth certificates represent an unbiased sample with respect to severity.

Overall, birth certificates showed minimal differences across patient subsets (Table 3). The average maternal age was slightly greater in the teaching setting. In the teaching setting, 12 (14%) of the women were 35 or older, and in the nonteaching setting, 21 (11%) women were in this age group. In both settings, the average patient had a similar number of previous pregnancies. The first visit occurred later in the teaching setting (0.4 months later, $P < .05$), but the teaching setting had a similar number of patient visits during the course of the pregnancy. We aggregated the problems of diabetes mellitus, hypertension, preeclampsia, eclampsia, herpes, epilepsy, and polyhydramnios into a composite measure of maternal case complexity. If a patient had any one of these conditions, her complexity score was rated 1, whereas if she had no complications, the rating was 0. The teaching setting had a significantly greater case complexity than the nonteaching setting. Of the cases in the teaching setting, 40% had some type of complicating condition during pregnancy, as opposed to 26% in the nonteaching setting. These characteristics of the patients' samples provided assurance that the teaching setting cared for patients likely, if anything, to be sicker than the patients in the nonteaching settings. An analysis of 1987 birth certificate data alone revealed no substantial differences from results for the combination of 1986 and 1987 data.

TABLE 3.—*Patient Characteristics (Averages) Based on Birth Certificate Data*

Patient Characteristics	Teaching Center (N = 84)*	Nonteaching Center (N = 202)†
Average maternal age, yr	28.9	28.0
Previous pregnancy, No.	1.44	1.46
Month of 1st visit	2.76	2.34‡
Prenatal visits, No.	11.2	12.6
Maternal case complexity§	0.40	0.26‡
Amniocentesis rate, %‖	31	6‡
Birth weight, grams (oz)	3,345 (118)	3,430 (121)
5-Min Apgar score <7, No.	1/84	2/202
Fetal death, No.	1/84	3/202

*Reflects 84 births from 83 mothers (1 twin birth).
†Reflects 202 births from 187 mothers (5 twin births).
‡Significant to $P < .05$.
§A composite measure of maternal case complexity comprises the following: The presence of diabetes mellitus, hypertension, preeclampsia, eclampsia, herpes, epilepsy, or polyhydramnios gives a score of 1; their absence gives a score of 0.
‖All "unknowns" were assigned to the "not done" category.

We also attempted to investigate physician practice patterns across various settings. In addition to data on cesarean deliveries, the only procedure-specific data available were on amniocenteses. Patients were significantly more likely to undergo amniocentesis in the teaching setting (31% versus 6%; $P < .001$). In the teaching setting, 58% of patients 35 years or older and 27% of patients younger than 35 years had an amniocentesis done. In the nonteaching setting, 33% of patients 35 years or older and 2% of patients younger than 35 years had an amniocentesis. In the teaching setting, 58% of the amniocenteses were performed for chromosome analysis; in the nonteaching setting, 82% were for chromosome analysis. The rest of these procedures were done in the final trimester for dating or other purposes.

Discussion

This study of maternal health care charges is unique in a number of respects. We have analyzed the academic center as an integrated system of care and have gathered all charge data for pregnancy and delivery in a comparable patient population. Charges were used in this study because in Washington State they serve as reasonable proxies for costs and because charges are important to the payers of health care—insurance companies, patients, employers, or governmental programs.

We chose to study prenatal and obstetric care because it met the requirements of being a time-limited "condition," having substantial inpatient and outpatient components, occurring commonly, and having the potential for physician variation in the method of treatment—that is, cesarean or vaginal delivery. In two previous studies, more prenatal tests were done in teaching settings, and, by implication, the costs were greater.[22,23] Furthermore, the lay press has noted higher charges for inpatient obstetric care in this teaching hospital and has quoted various publicly available sources to demonstrate these price differences (Washington State Hospital Commission[24]; R. Hibbard, "Shopping for a Hospital—Report Reveals Wide Differences in Costs," *Seattle Post Intelligencer*, June 9, 1987, p 1). For example, in the western region of Washington State in 1985 to 1987, the teaching hospital had the highest inpatient charges for each maternity-

related DRG (DRGs 370 to 374). If we averaged the inpatient charges across these DRGs (to control for different rates of cesarean deliveries), the teaching hospital appeared to be much more expensive on a per-patient basis ($2,564 [N = 2,955] versus $1,945 [N = 19,539]). Had we drawn inferences based solely on publicly available hospital inpatient charge data, we would have concluded that the teaching setting provides more costly care. In our study, however, we analyzed a comparable patient population and showed that the difference in charges between settings is minimal when either total charges or only inpatient hospital charges are evaluated.

We analyzed all charges associated with obstetric care. We found that 54% of the total charges for vaginal deliveries were the result of inpatient care whereas 60% of the total charges for cesarean deliveries were the result of inpatient care. These findings are consistent with the observations of Fuchs and Perreault who showed that, in 1983, 56% and 62% of total charges were associated with inpatient charges for vaginal deliveries and cesarean deliveries, respectively.[25] This suggests that the charge pattern for obstetric care in Washington State is consistent with that at the national level.

Although the charge for a delivery in the teaching setting was relatively more expensive for each component—cesarean deliveries, vaginal deliveries, and inpatient and outpatient components—the nature of the difference in practice patterns, specifically, the lower rate of cesarean deliveries in the teaching setting, canceled out these higher charges and yielded overall mean charges that did not differ significantly from those of the nonteaching setting. In addition, while we cannot be certain that the lower rate in the teaching setting indicates more appropriate cesarean sections, it is consistent with the findings of Brook and co-workers that there was a higher level of "appropriate" surgical procedures in the teaching centers.[26] Although it could be hypothesized that private settings saw patients who are more "in need" of cesarean deliveries, the birth certificate data do not support such an explanation. In fact, the maternal case-complexity category on the birth certificates indicated that the teaching setting cared for more complex patients than the nonteaching setting. Without a complete chart review, however, we are reluctant to conclude that the teaching patients are necessarily "sicker," but it is reasonable to conclude that the teaching setting did not have less complex patients.

We had limited information on the pattern of care in each setting during the course of the pregnancies. The average number of prenatal visits in each center was similar and consistent with the recommendations of the American College of Obstetricians and Gynecologists.[27(pp17-18)] The data that indicated higher rates of amniocentesis in the teaching setting were consistent with previous studies that showed increased obstetric-related test ordering in the teaching setting.[22,23] In our study, this was not associated with higher charges.

This study has a number of limitations: the small number of patients (425), the analysis of only one type of medical care (obstetrics), the analysis of care in only one geographic region, and the analysis of care in only one time period. In addition, a concern might be that one group might have selected a certain care provider knowing beforehand the type of care they would be more likely to receive, such as amniocentesis or cesarean deliveries. Because this was the first study that has dealt with the issue in these specific hospitals, this is unlikely to have been a factor with the patients in this investigation.

Naturally it is difficult to generalize from obstetrics to other medical conditions. For its total enrolled population, however, this teaching setting has a ratio of capitation payments to charges that is similar to or higher than that of other multispecialty clinics in the area that participate in this HMO network. This implies that the cost competitiveness of the teaching setting is not primarily due to a lower payment for a given charge in the teaching setting relative to the nonteaching setting, but that the costs of care on a population-based level are comparable. Furthermore, there is no evidence that in this teaching setting, HMO patients are subsidized relative to other patients. Hence, obstetric patients may not represent a unique situation for the teaching setting.

Care should be exercised when interpreting our results in policy discussions regarding the need for indirect cost adjustments for teaching hospitals, such as those provided by Medicare. This study addressed treatment patterns and charges for similar patients and excluded impoverished, uninsured patients who traditionally use more resources than insured patients.[28] This study had an 80% power to detect a difference of 6% in charges between the settings. Thus, it is unlikely that we failed to detect a 7.8% cost increase for teaching over nonteaching settings—the Medicare allowance for the indirect costs associated with teaching hospitals. Although our study indicated that similar patients can be treated for similar charges in teaching and nonteaching institutions, these teaching institutions traditionally attract patients who have more severe illnesses or who are less able to pay. We think indirect reimbursement should cover these costs unless other ways are found to pay for them at a societal level.

Future studies need to address other issues with respect to overall care. These studies could include such problems as the evaluation of patients presenting with chest pain, abdominal pain, or back pain and should include costs for all subsequent care provided to that cohort, rather than concentrating separately on surgical versus medical patients, or hospital costs based on final diagnosis. An evaluation of the total costs of care starting with the initial outpatient workup will provide more appropriate cost comparisons than merely analyzing the costs of certain procedures or DRGs.

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ANEURYSM

Lilacs bloomed white that spring day
when you left us for the world of pale,
tired surgeons with their microscopic drills and saws,
peeling back worry wrinkles to the thinnest core,
exposing your most delicate hardware
pausing at the display:
There's lust.
There's motivation.
There's intelligence.

I recall, before they opened you,
the elevator ride down to the hospital bowels.
The grim, suspended feeling these journeys
take on. The way rapid events slow to a muffled
stillness. The way my voice and fingers
become your last connection of past, when I hand you
to the jolly anesthesiologist who had seen it all.
He applies the final curtain of drugs. Your eyes
flutter, close, then open wide for a moment as you slip
into your new life. Then you are gone.
A pretty Japanese doctor hands me a styrofoam cup
of burning coffee which I drink in one memorable
swallow to slow the shaking.

I begin to believe aneurysms are common occurrences,
similar to crimson tonsils, plugged ears, twisted ankles,
that this Catholic hospital of the sacred heart ticks
with leaky blood vessels, defective brain gear, glorious
transformations. I could say *medical wonders,*
but the body is the miracle.
Nobody ever leaves this place the same.
And before? "We never know what they were like
before they got here," laughs a nurse.

STEPHEN LYONS©
Moscow, Idaho

Conferences and Reviews

Hemobilia—Evolution of Current Diagnosis and Treatment

STEVEN W. MERRELL, MD, *Rochester, Minnesota; and* PHILIP D. SCHNEIDER, MD, PhD, *Sacramento, California*

"Hemobilia," upper gastrointestinal tract bleeding that originates from within the biliary tract, has become widely recognized due to an increased clinical awareness of the disorder and to improvements in diagnostic techniques. In addition, the growing use of percutaneous liver puncture for the diagnosis of and therapy for hepatobiliary diseases and the increased incidence of both blunt and penetrating hepatic trauma have contributed to a rising incidence of hemobilia. We review the history, pathophysiology, and current approaches to the diagnosis and treatment of this disease.

(Merrell SW, Schneider PD: Hemobilia—Evolution of current diagnosis and treatment. West J Med 1991 Dec; 155:621-625)

In his extensive review of hemobilia in 1972,[1] Sandblom credits Francis Glisson with the first reported case of hemobilia.[2] In 1654, Glisson described the clinical course of a young nobleman who was stabbed with a sword in the right upper quadrant and died following massive upper gastrointestinal hemorrhage. At postmortem examination, the young man's bleeding was found to originate from a deep laceration of the liver. Glisson used his knowledge of liver anatomy to propose a pathogenetic mechanism for the bleeding: "[T]here is no doubt that the bile ducts take unto themselves (to the great good of the patient) blood issuing from the liver. From there it is either impelled upwards through reverse peristalsis, or downwards in the normal way."[2]

Scattered case reports of biliary tract hemorrhage appeared over the next 100 years, but all were diagnosed postmortem.[1] In 1777, Antoine Portal was the first to recognize a case of hemobilia antemortem.[3] The vigorous application of leeches and serial bloodlettings were unsuccessful, and the patient died. Quincke described a case of hemobilia in 1871, emphasizing the characteristic clinical features of right upper quadrant pain, jaundice, and upper gastrointestinal tract bleeding. These signs and symptoms are now recognized by modern authors as the components of the classic clinical "triad."[4]

The first surgical approach to hemobilia was reported in 1895, when a total gastrectomy was done but was not effective in controlling the patient's hemorrhage. The patient died five days later.[5] This was the first of numerous inappropriate surgical procedures performed for hemobilia. Surgeons have attempted such procedures as cholecystectomy, antireflux procedures, fecal diversion, and colon resection in an attempt to stop the bleeding of hemobilia, with predictably bad results.[1] The imprecision of diagnostic techniques in the distant past led to misguided operative decisions made in the face of threatened exsanguination.

In the first successful (and appropriate) operation for hemobilia, Kehr in 1903 identified an aneurysm of the right hepatic artery that had ruptured into the gallbladder neck, and he treated the lesion by direct arterial ligation.[6] The first successful hepatic resection for hemobilia was not reported until 1957.[7] This hepatic resection was done only after a gastric resection and subsequent cholecystectomy had failed to control the patient's hemorrhage!

The term "hemobilia" was first coined by Sandblom in his 1948 paper entitled "Hemorrhage into the Biliary Tract Following Trauma: Traumatic Hemobilia."[8] In 1971, Sandblom published his collected works on hemobilia in the first and only book devoted entirely to this subject.[1] A few years later, Walter was the first to use angiographic embolization for the treatment of this disease,[9] a modality that has since become the mainstay of treatment in most cases of hemobilia.[10-13]

Etiology

Hemobilia may occur in a variety of settings, including trauma, cholelithiasis, acalculous inflammatory diseases, vascular disorders, and neoplasms, in descending order of reported frequency (Table 1).[1,14,15]

Posttraumatic hemobilia is the most common etiologic category, accounting for 55% of cases in Sandblom's collected series[1] and 40% to 85% of cases in more recent reports that reflect a rise in the incidence of blunt and penetrating liver injury due to violent crime and vehicular accidents and the increased use of percutaneous biopsy and intubation techniques for managing hepatobiliary diseases.[13-15] The liver is the most commonly injured abdominal organ,[16] and hemobilia may complicate the clinical course of as many as 3% of patients with substantial liver injuries.[1,14,17,18] In two recent

TABLE 1.—*Causes of Hemobilia*

	Patients, No. (%), by Source			
Cause	*Sandblom* (n=355)*	*Curet† (n=86)*	*Yoshida‡ (n=103)*	*Collected Series (n=544)*
Iatrogenic trauma	59 (17)	50 (58)	42 (41)	151 (28)
Accidental trauma	137 (38)	23 (27)	20 (19)	180 (33)
Gallstones	53 (15)	--	9 (9)	62 (11)
Acalculous inflammation	46 (13)	--	10 (10)	56 (10)
Vascular conditions	38 (11)	--	15 (14)	53 (10)
Neoplastic disease	22 (6)	--	7 (7)	29 (5)
Unspecified atraumatic	--	13 (15)	--	13 (2)

*From Sandblom.[1]
†From Curet et al.[14]
‡From Yoshida et al.[15]

From the Department of Surgery, University of Utah School of Medicine, Salt Lake City (Dr Merrell), and the Department of Surgery, University of California, Davis, School of Medicine, Sacramento (Dr Schneider). Dr Merrell is now with the Section of Vascular Surgery, Mayo Clinic, Rochester, Minnesota.

Reprint requests to Philip D. Schneider, MD, PhD, Department of Surgery, University of California, Davis, School of Medicine, 4301 X St, Sacramento, CA 95817.

series, 83% to 95% of cases of traumatic hemobilia occurred after blunt injury.[14,15] This finding is likely due to the fact that penetrating injuries are usually explored primarily at the time of injury and adequately treated at the initial operation. Posttraumatic bile stasis, hematomas, and abscesses all predispose to the development of hemobilia. Based on the experience with children who have sustained trauma,[17] there is a trend toward the initial nonoperative management of blunt injuries in adults, and one might expect an increased incidence of hemobilia with a more widespread application of this strategy.

Iatrogenic hemobilia may occur from percutaneous liver procedures, liver or biliary operations, or therapeutic anticoagulation. The use of percutaneous liver puncture for biopsy, cholangiography, and drainage of the biliary tract has become common, sparing many patients open surgical procedures for the diagnosis and management of some hepatic diseases.[13-15,19-24] These procedures, however, are the equivalent of a penetrating liver injury that is treated nonoperatively. Given the close proximity of bile duct radicals to the branches of the hepatic artery and portal vein, the substantial incidence of concurrent injury to these structures and fistula formation is not unexpected. A 3.8% incidence of hepatic vascular abnormalities was found following percutaneous transhepatic cholangiography, a 5.4% incidence of hepatic vascular abnormalities following percutaneous liver biopsy, and a 26.2% incidence following the placement of indwelling transhepatic drainage catheters.[25] These findings were confirmed in 1980 in patients with drainage catheters.[26] The frequency of clinical hemobilia ranges from less than 1% for liver biopsy[19,20] to 4% for transhepatic cholangiography[23] and 3% to 14% for percutaneous transhepatic catheter drainage.[21,22] The incidence appears to increase with larger caliber instruments, central liver punctures, and indwelling catheters (which may cause pressure necrosis of adjacent blood vessels). Iatrogenic hemobilia may also occur after operations on the liver or biliary tract,[1,13,24,27,28] and there is a single report of iatrogenic hemobilia occurring in a series of patients following the placement of indwelling hepatic artery catheters.[27] Finally, biliary bleeding has been reported as one of the iatrogenic complications of therapeutic anticoagulation.[24]

Figure 1.—This patient had hemobilia develop after a common bile duct exploration. Her celiac angiogram showed a pseudoaneurysm in the gastroduodenal artery (arrow), but the location was felt to be unsafe for embolization because of technical problems encountered while attempting to occlude the vessel. The pseudoaneurysm was ligated during celiotomy, and the patient has had no recurrent bleeding (case courtesy of Richard Price, MD, and Robert Ghelfi, MD).

Upper gastrointestinal tract bleeding due to gallstones accounts for 9% to 15% of all reported cases of hemobilia.[1,15] Unlike in posttraumatic cases, bleeding in this setting is more likely to be minor. Occult rectal bleeding classically was thought to be a physical sign of cholelithiasis and may occur in as many as 37% of all patients with gallstones.[1,29] Hemorrhage may result from direct mucosal erosion or from hemorrhagic necrosis complicating severe cholecystitis or cholangitis.[13,29]

Acalculous inflammatory conditions of the biliary tract are implicated in 10% to 13% of reported hemobilia cases.[1,15] This cause accounts for a higher proportion of cases in underdeveloped countries, where parasitic diseases are more prevalent and violent crime or high-speed blunt trauma are relatively less common. The leading cause of hemobilia in this category is ascariasis, a disease with an estimated worldwide prevalence of 25% and a striking propensity to infest the biliary tract.[30] Hemobilia may also complicate the clinical course of hepatic abscess, acalculous cholecystitis, and cholangitis.[1,31,32] Rare cases of biliary hemorrhage have been reported with hepatitis, pancreatitis, and chemical inflammation or erosion due to heterotopic stomach.[1,33]

Primary vascular causes of hemobilia have been identified in 11% to 15% of cases.[1,15] The differential diagnosis in this area includes aneurysmal disease of the hepatic artery or portal vein or vasculitis.[1,7,13,34-36] Portal hypertension has traditionally been cited as a vascular cause of hemobilia,[1] but only five cases of spontaneous biliary hemorrhage from the portal circulation have been reported,[36-38(p102),39] and all but one originated from extrahepatic sources.[39] Portal hypertension is more likely to be a predisposing factor for bleeding after accidental or iatrogenic trauma rather than a primary cause.[34,39] Biliary hemorrhage from vascular sources tends to be massive and life-threatening.

The last major cause of hemobilia is neoplastic disease, accounting for 6% of cases reported.[1,15] Most cases occur because of hepatocellular carcinoma, although fibrolamellar hepatoma, hemangiomas, cholangiocarcinoma, gallbladder carcinoma, and even adenocarcinoma of the pancreas may rarely cause biliary hemorrhage.[1,40,41] Benign lesions of the bile ducts and gallbladder and tumors metastatic to the liver or biliary tract are also rarely associated with hemobilia.[1,42-44] Hemobilia from these sources tends to present as chronic anemia.

Diagnosis

The clinical presentation of hemobilia includes biliary colic in 70% of patients, jaundice in 60%, and gastrointestinal bleeding in all patients, although this may range from occult to massive bleeding.[1] The classic triad of pain, jaundice, and bleeding is present in only 32% to 40% of patients.[13-15] Yoshida and colleagues reported that the initial diagnosis was made with angiography (28%), endoscopy (12%), intraoperatively (34%), and with the noting of blood in various biliary drains (12%).[15] Anecdotal reports indicate that technetium-labeled erythrocyte scans and the presence

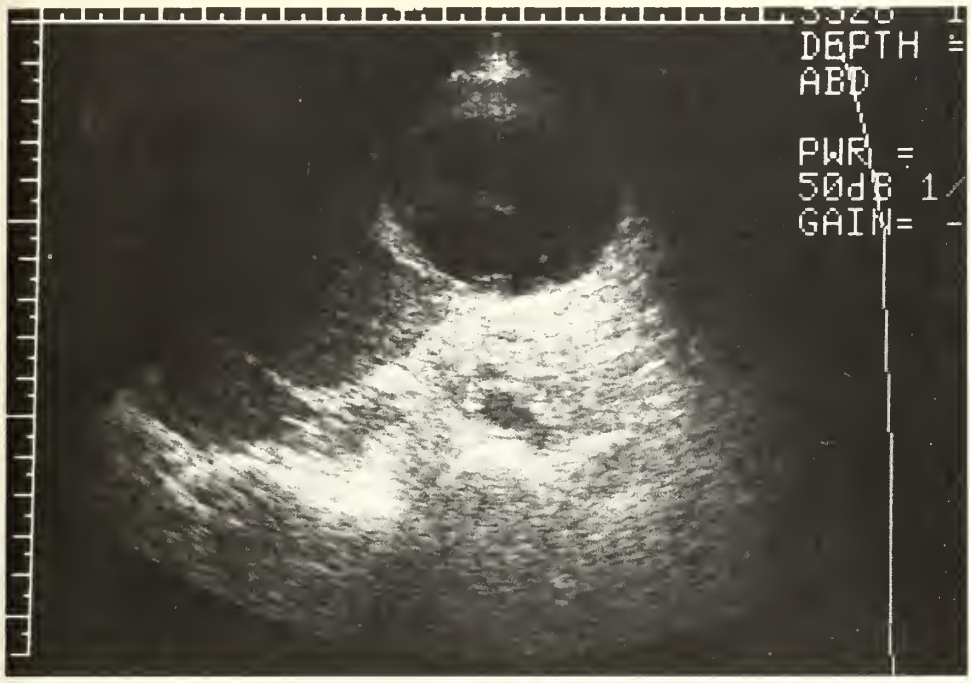

Figure 2.—An ultrasonogram shows a cystic mass in the gallbladder, which was the only abnormality identified during preoperative evaluation of a patient with hemobilia. The patient underwent cholecystectomy, but the cystic mass was an organized blood clot. The patient was later found to have a hepatic source for the hemobilia (reprinted with permission from Merrell et al[39]).

of fecal occult blood occasionally support or suggest the diagnosis,[45] but a reliance on these tests for diagnosis cannot be justified.

Angiography is the most useful diagnostic and therapeutic modality, but it is not always successful (Figure 1).[9-15,46] The variable rate and intermittent nature of bleeding may hinder diagnosis. Furthermore, anomalous, atherosclerotic, or tortuous vessels or a previous hepatic artery ligation may limit access to the arterial supply of the liver or bile ducts.[13] The chief virtue of angiography is that diagnosis can be combined with therapeutic embolization, the treatment of choice for most cases of hemobilia.

Other methods of diagnosis may include computed tomography and ultrasonography. Computed tomography is useful in cases of liver trauma and may help identify hematomas and bile collections or deep parenchymal disruptions that could predispose to hemobilia.[14,16,17] Ultrasonography may also be helpful in the diagnosis of hemobilia, but it is nonspecific. Abnormalities seen on ultrasound examinations may or may not be causing hemobilia or may be the result of hemobilia (for instance, blood clots in the gallbladder) (Figure 2).[14,39,47,48]

Hemobilia is more frequently being diagnosed endoscopically.[15,27,49,50] Although only 12% of cases are initially diagnosed with endoscopy, it may confirm the diagnosis in an additional 30% of patients and help exclude other causes of upper gastrointestinal tract bleeding.[15,27] Endoscopic access to the biliary system through percutaneous tube tracts has also been successfully used for the laser coagulation of biliary bleeding.[51] With the development of biliary endoscopes, the increasing use of nasobiliary catheters, and endoscopic sphincterotomy, endoscopic procedures may become increasingly important in the diagnosis and therapeutic management of hemobilia.[50]

If all of these measures fail to provide a diagnosis, or if the patient presents under emergency circumstances with hemodynamic instability, the surgeon may be forced to do an exploration without a precise preoperative diagnosis. Active bleeding from the duodenum may be apparent following a gastrotomy or may be detected by a rapid filling of the proximal small bowel after portioning into segments with Penrose drain "tourniquets."[39] Occasionally a lateral duodenotomy may show the expulsion of vermiform clots from the ampulla. Finally, intraoperative cholangiograms may show filling defects in the bile ducts and confirm the diagnosis (Figure 3).

Pathophysiology

A spectrum of presentations is possible: Bleeding may be either scanty or profuse, prolonged or brief, continuous or intermittent. Hemobilia may arise from any anatomic site that communicates with the biliary system (Table 2).[1,14,19] The fate of clots in the biliary tree may involve one of four possibilities: dissolution, spontaneous expulsion from the biliary tree, a combination of dissolution and expulsion, or persistence within the biliary system.[1,27,52] Acute biliary obstruction by clot may cause cholangitis, cholecystitis, or pancreatitis.[1,32] Also, symptomatic hemobilia due to biliary obstruction may result not only from blood clots but from fibrin clots, or leukocyte-fibrin clots. Furthermore, clot that remains in the bile ducts for long periods of time may serve as a nidus for gallstone formation.[53]

Through several simple but elegant experiments that were correlated with careful clinical observations, the differences in biochemical characteristics of bile and blood and the influ-

TABLE 2.—*Anatomic Origin of Hemobilia*

Site of Origin	Patients, No. (%), by Source: Sandblom* (n=355)	Yoshido† (n=103)	Collected Series (n=458)
Liver	187 (53)	70 (68)	257 (56)
Extrahepatic bile ducts	80 (22)	22 (21)	102 (22)
Gallbladder	82 (23)	9 (9)	91 (20)
Pancreas	6 (2)	2 (2)	8 (2)

*From Sandblom.1
†From Yoshida et al.15

ence of bile on wound healing in the liver were studied.[52,54] In the course of these experiments, blood and bile were found to have different specific gravities: 1.005 and 1.010, respectively. Measurements of surface tension disclosed that the surface tension of blood is 60 dynes per cm compared with 40 dynes per cm for bile. This difference is sufficient to allow a stable interface to form under some circumstances.[51] In a series of experiments using an in vitro model of the biliary tree, Sandblom and co-workers were able to simulate the conditions of blood mixing in bile and postulated mechanisms for the genesis of biliary symptoms related to hemobilia.[29,55] The rapid mixing of blood with bile created a dispersion in which no discrete clots developed. The resultant coagulum was characterized as "mushy" and "sticky." In contrast, during the slow injection of fresh blood into flowing bile, there was no mixing and pure clots formed. The differing specific gravities and surface tensions of blood and bile likely accounted for this phenomenon. In addition, clot organization resulted in an additional decrease in blood specific gravity, allowing clots to float.

In studies of the fibrinolytic properties of bile in vitro, clot lysis occurred only with warm bile, which suggested an enzymatic mechanism. It was also found that clot lysis required bile flow past the clot. This flow dependence of fibrinolysis was confirmed in an animal model.[52]

In experiments on the healing of liver wounds, fibrin production, granulation tissue formation, and scarring were diminished in the presence of bile.[54] Sandblom and colleagues postulated that the exposure of liver injuries to pooled bile slowed overall wound healing and prolonged the risk period for the genesis of hemobilia.

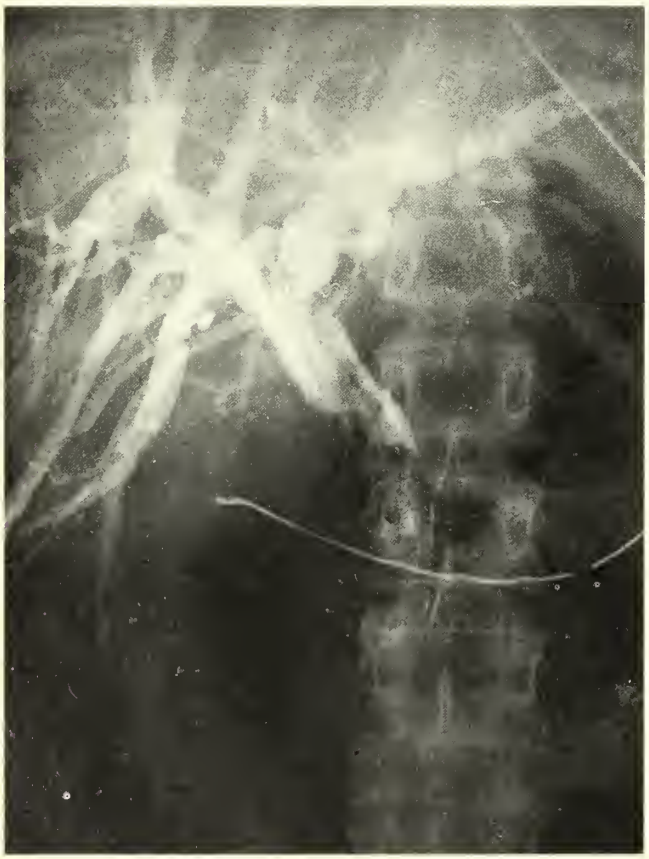

Figure 3.—A transduodenal cholangiogram shows many filling defects in the common bile duct with proximal ductal dilatation. The filling defects represent blood clots from hepatic hemobilia (reprinted with permission from Merrell et al[39]).

Several clinical correlates of these experimental findings were recognized. Slow bleeding was more likely to be associated with the formation of durable clots and biliary obstruction. Because clot lysis requires bile flow, biliary diversion through a T tube, in the presence of ampullary stenosis, contributed to distal common duct stasis and clot persistence. Filling defects seen on cholangiograms could well represent blood clots rather than stones, especially if they were floating.[55] It was thought that clots have the potential to cause late stone formation as a result of pigment deposition, encrustation, or calcification. Finally, ensuring adequate biliary tract drainage or the drainage of liver lacerations following hepatic trauma could decrease bile pooling, promote healing, and reduce the risk of hemobilia.

Therapy

The goals of therapy in cases of hemobilia are to stop the bleeding and to restore bile flow past clots. Modalities used to stop bleeding include angiography with embolization, surgical intervention, observation, and electrocoagulation or photocoagulation. Angiography is clearly the most efficacious method for controlling intrahepatic bleeding sources, with success rates above 95%.[11-15,46] In the past, the successful embolization of extrahepatic bleeding sites was hampered by the technical inability to gain sufficiently selective arterial access, leading to complications caused by nonselective embolization. For anatomic reasons, most authors have advocated surgical therapy for extrahepatic hemobilia. More recently, angiographic embolization has been shown to be useful for the control of extrahepatic bleeding even after surgical failure.[15] Some causes of extrahepatic bleeding may lend themselves to surgical correction such as bile duct tumors or bleeding from the gallbladder mucosa. Therefore, the cause of bleeding should be considered in planning therapy. But technical features of such cases, such as scarring from a previous operation, may limit surgical effectiveness. Thus, the specific anatomy should be carefully evaluated in cases of hemobilia from extrahepatic sites, and embolization should be considered when it appears the safest method and technically possible.[13]

Although surgical treatment is highly successful in controlling intrahepatic hemobilia after failed transcatheter embolization, it does not approach the success rate of transcatheter embolization as the initial treatment.[15] In one series, surgical treatment led to the successful control of 77% of hemobilia cases when hemobilia arose from extrahepatic sources.[15] Angiographic techniques, however, were successful in two cases of extrahepatic hemobilia when it was attempted as initial therapy. This confirms that embolization is useful in the management of selected patients with extrahepatic hemobilia when vessel ligation fails.

Surgical therapy may be most helpful in cases of hemobilia after blunt liver trauma for which debridement, drainage, and vessel ligation are important.[1,27] Studies of liver healing in patients with substantial hepatic trauma would support the placement of drains to reduce the possibility of bile pooling.[54] The performance of selective hepatic artery ligation is a surgical maneuver that may be useful in occasional hemobilia cases.[13] It is interesting to note that hemobilia from a portal venous source, though exceedingly rare, is likely to require surgical treatment.[28] Finally, surgical therapy should

be considered the treatment of choice when the underlying cause of hemobilia constitutes an independent indication for such treatment, such as cases associated with cholelithiasis, cholecystitis, or resectable neoplasms. Although an operation carries an obvious risk of morbidity, transcatheter embolization is not without substantial risk. Hepatobiliary necrosis (6%), abscess formation (9%), bleeding (6%), and gallbladder fibrosis (2%) have occurred following arterial embolization.[11-15]

The last commonly used therapeutic option for managing hemobilia is that of expectant observation. Spontaneous cessation of bleeding occurs most commonly in patients who undergo percutaneous cholangiography or liver biopsy; therefore, this group merits observation as primary management. Some authors have proposed the prophylactic administration of clot promoters such as absorbable gelatin sponges (Gelfoam, Upjohn, Kalamazoo, Michigan) into percutaneous puncture tracts during withdrawal of the instruments or drains from the liver as a means of reducing the frequency of bleeding complications.[25,26]

Endoscopic techniques for controlling hemorrhage and managing clots include nasobiliary drainage, endoscopic sphincterotomy, and laser photocoagulation using small endoscopes placed through a catheter tract with access to the biliary tree.[15,49-51] These methods have only been reported anecdotally and will probably continue to have a role in a selected few patients.

Summary

The successful diagnosis of hemobilia depends on a high index of suspicion, especially when the common causes of upper gastrointestinal tract hemorrhage have been excluded. A clinical suspicion should prompt confirmation of the diagnosis with angiography or endoscopy, but computed tomography or ultrasonography may also be helpful. Careful consideration of the specific anatomy will help define the therapeutic options—angiography versus surgical intervention. If access is available to the biliary tree through a percutaneous tube tract, the possibility for successful electrocoagulation or photocoagulation exists using biliary endoscopy. In occasional cases, all preoperative studies may be negative, and surgical exploration may provide the only diagnostic and therapeutic option.

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Status Epilepticus

Clinical Features, Pathophysiology, and Treatment

CRAIG WATSON, MD, PhD, *Sacramento, California*

During the past two decades, substantial progress has been made in the understanding of the clinical features, classification, pathophysiology, central nervous system consequences, and treatment of status epilepticus. The most commonly used drug regimens have advantages and disadvantages, and, in this review, I recommend a protocol for the treatment of status epilepticus. An important concept in the approach to patients in generalized tonic-clonic status epilepticus is that treatment should be administered within a predetermined time frame. Clinical and experimental research indicates that continuous seizure activity for longer than 60 to 90 minutes may result in irreversible brain damage. As our understanding of the basic mechanisms of neuronal function and seizure generation advances, it is expected that more specific and novel approaches to the treatment of status epilepticus will emerge.

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Generalized convulsive (tonic-clonic) status epilepticus is a medical emergency. Unless prompt and appropriate treatment is given, generalized tonic-clonic status epilepticus can lead to profound, life-threatening metabolic and physiologic disturbances. There is also increasing evidence that the repeated seizures that constitute status epilepticus can cause prolonged brain dysfunction and even neuronal death.

Definition and Classification

Status epilepticus can be defined as a state of continuing or recurring seizures in which recovery between attacks is incomplete—that is, a series of seizures without regaining consciousness between attacks. The official definition is that status epilepticus is "a condition characterized by an epileptic seizure that is sufficiently prolonged or repeated at sufficiently brief intervals so as to produce an unvarying and enduring epileptic condition."[1(p72),2] As will be seen later, status epilepticus might be defined pathophysiologically as any seizure activity lasting 30 minutes or longer.

Status epilepticus can occur with any seizure type, and therefore one may speak of generalized tonic-clonic status, absence status, complex partial status, or simple partial (focal) status (Table 1).[3] The only true emergency among these is generalized tonic-clonic status epilepticus, although any type should be terminated as quickly as possible. Aggressive therapy, however, as will be described, has its own risks and therefore must always be weighed against the possible benefits when treating a less than urgent form of this condition.

Epidemiology

It is estimated that about 60,000 cases of generalized tonic-clonic status epilepticus occur in the United States each year.[4] About a third of these cases consist of the first seizure in patients in whom recurrent seizures or epilepsy will develop. Another third of the cases occur in patients with an established diagnosis of epilepsy, and the other third of cases develop in patients without a history of epilepsy.[4]

Status epilepticus occurs most frequently in children but also is frequent in patients older than 60 years. The mortality related to the seizures per se consists of approximately 1% to 2%, whereas the mortality related to the underlying illness causing the status epilepticus is about 10%.[4,5]

Etiology

The reported causes of status epilepticus vary from study to study. They mainly reflect referral patterns within communities and therefore are dependent on the institution at which the study was conducted. Common causes of status

TABLE 1.—*Classification of Status Epilepticus*

Class	*Type*
Generalized convulsive status epilepticus	Tonic-clonic Tonic Clonic Myoclonic
Generalized nonconvulsive status epilepticus	Absence
Simple partial (focal) status epilepticus	Somatomotor—epilepsia partialis continua Sensory—somatosensory, special sensory Aphasic Autonomic
Complex partial status epilepticus	

From the Department of Neurology, University of California, Davis, School of Medicine, Davis, and the Sutter Neuroscience Center Epilepsy Program and Sacramento Comprehensive Epilepsy Program, Sacramento, California.

Reprint requests to Craig Watson, MD, PhD, 2600 Capitol Ave, Suite 211, Sacramento, CA 95816.

ABBREVIATIONS USED IN TEXT

CNS = central nervous system
ECG = electrocardiogram
EEG = electroencephalogram/phic
IV = intravenous

epilepticus include head trauma, tumor, stroke, central nervous system (CNS) infection, drug and alcohol abuse and withdrawal, congenital CNS abnormalities, fever in children, acute systemic and metabolic illnesses, and antiepileptic drug noncompliance in patients with epilepsy. In about 15% to 30% of cases, no cause can be identified, resulting in a diagnosis of idiopathic status epilepticus. A considerable proportion of cases of status epilepticus occur in the context of an acute insult or injury, regardless of whether the patient has a previous history of epilepsy or another neurologic disorder.[4,6,7]

Morbidity and Mortality

Morbidity and mortality from status epilepticus seem to be related to three factors: CNS damage due to the underlying illness or acute insult causing the status epilepticus, CNS damage caused by repetitive electrical discharges of the seizures themselves, and systemic and metabolic factors related to repeated generalized tonic-clonic seizures.[5] Death associated with status epilepticus most often is related to the underlying illness rather than the seizures themselves.

In recent years, studies have shown that seizures lasting longer than 60 to 90 minutes may result in neuronal death in patients with generalized tonic-clonic seizures and in those with epilepsia partialis continua.[8-11] Furthermore, prolonged memory deficits have been recorded after complex partial status epilepticus.[12-14] Others have reported that prolonged febrile, and perhaps nonfebrile, seizures occurring between the ages of 6 months and 7 years may result in damage to the hippocampus (hippocampal sclerosis) and thereby contribute to recurrent complex partial seizures of temporal lobe origin.[15-18]

The systemic and metabolic effects of repeated generalized tonic-clonic seizures involve the cardiovascular, respiratory, renal, metabolic, and autonomic nervous systems. Cardiovascular changes in response to status epilepticus include tachycardia or bradycardia, arrhythmias, and hypotension. Respiratory failure may be precipitated by the acute underlying illness or pulmonary edema and may be complicated by antiepileptic drug administration in the treatment of this disorder. Generalized tonic-clonic seizures may rarely result in rhabdomyolysis with resultant myoglobinuria and acute renal failure. Metabolic complications include respiratory and metabolic acidosis, hypoxia, hyperkalemia, hypoglycemia, and pronounced increases in serum levels of prolactin, glucagon, insulin, norepinephrine, epinephrine, growth hormone, and cortisol. Autonomic nervous system effects can include hyperpyrexia, increased sweating, increased tracheobronchial secretions, pupillary dilation or constriction, and cardiovascular complications, as mentioned earlier.[5,7,19-23]

TABLE 2.—*Electroencephalographic Patterns in Status Epilepticus**

Discrete seizures with interictal slowing
Waxing and waning of ictal discharges
Continuous ictal discharges
Continuous ictal discharges punctuated by flat periods
Periodic epileptiform discharges on a flat background

*From Treiman.29

Pathophysiology

In considering the pathophysiology of status epilepticus, three general principles have been described:

- Status epilepticus appears to have a distinct natural history and evolution.
- The more prolonged status epilepticus becomes, the more intractable it is to effective treatment.
- The more prolonged the status epilepticus, the more likely it is associated with a poor prognosis.[7,24-26]

Natural History of Status Epilepticus

A number of investigators, studying status epilepticus mainly in animals but also in humans, have described a sequence of events that evolve over a fairly predictable time course. These events can be categorized as electroencephalographic (EEG), motor, and systemic.

Electroencephalographic stages. Treiman and colleagues have described a series of five EEG patterns in status epilepticus (Table 2).[27-29] This sequence of progressive EEG changes has also been described in animal models of status epilepticus provoked by electrical stimulation of the brain.[30,31] In the initial stage, the EEG shows discrete seizures with interictal slowing. As the condition continues, the discrete seizure pattern first begins to wax and wane and then evolves into a stage of continuous ictal discharges. If seizures persist, ictal discharges are interrupted by flat periods in the EEG background, and, in the end stage, paroxysmal bursts of epileptiform discharges arise out of a flat background.

Motor stages. The evolution of motor activity during status epilepticus correlates roughly with that of the EEG. At the start, patients usually undergo discrete seizures that correspond to the discrete episodes of ictal discharges on the EEG. Between seizures there is interictal slowing, and the patient does not recover consciousness. As status epilepticus continues, the seizures may wax and wane and then merge into continuous generalized clonic activity that also is reflected in the EEG. After status epilepticus has persisted for about an hour, motor activity may begin to diminish even though seizure activity continues to be shown on the EEG. In the last stages of status epilepticus, motor activity may actually disappear but the EEG continues to show periodic epileptiform discharges. Treiman and associates speak of an "electromechanical dissociation" between the motor events and the EEG discharges during this stage.[28]

Systemic and metabolic stages. A number of metabolic and systemic effects have been reported during status epilepticus and have been divided into two phases. The first phase usually lasts about 30 minutes and is associated with an increase in blood pressure with each seizure, an increase in serum lactate and serum glucose levels, and a decrease in serum pH resulting in acidosis. As the transition into the second phase at about 30 minutes occurs, the blood pressure tends to return to normal—the patient may even become hypotensive—and no longer responds with an increase with each seizure. Serum pH and lactate values also return to

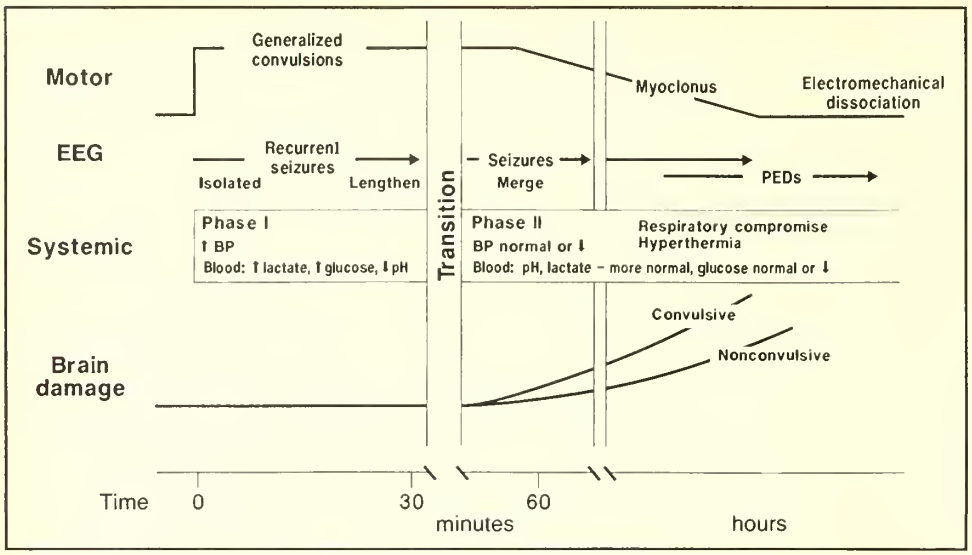

Figure 1.—The diagram shows the evolution of pathophysiologic changes during status epilepticus (adapted with permission from Lothman[25]). BP = blood pressure, EEG = electroencephalographic, PEDs = periodic epileptiform discharges

normal, and the glucose level may become normal or low. As status epilepticus progresses through a second transition period after about 60 minutes, respiratory compromise and hyperthermia occur and the degree of status epilepticus-induced brain damage increases.[8,10,19]

Figure 1 summarizes the pathophysiologic changes in diagrammatic form.[25] This information was obtained from studies using both primates and rodents as well as more limited information from human studies.

Central Nervous System Consequences of Prolonged Status Epilepticus

As mentioned, clinical experience indicates that the longer status epilepticus continues, the more difficult it is to treat and the poorer the prognosis. These observations have been verified in studies of animals. There appears to be a critical "transition period" of 30 to 60 minutes for the duration of status epilepticus. After this period of time, the seizures become more refractory to treatment, and the likelihood of prolonged or even permanent brain damage is greater.

Work with animals has shown that prolonged seizures in primates result in damage in five areas of the brain. These include layers 3, 5, and 6 of the cerebral cortex, the cerebellum, the hippocampus, certain thalamic nuclei, and the amygdaloid body.[8,10] If, however, the animals are protected against the systemic and metabolic effects of status epilepticus by artificial respiratory support and paralyzation, damage involves mainly the hippocampus with partial sparing of the other areas.[9,10,32] This observation has been verified using similar techniques in several species of animals. It appears likely, therefore, that prolonged seizures can cause at least hippocampal damage, especially if the seizures are generalized tonic-clonic. Some degree of CNS damage can occur, however, even if the seizures are nonconvulsive in nature.[10,32-41]

It has also been shown that spontaneous recurring seizures occur in animals as a chronic sequela to an episode of status epilepticus.[37,42,43] This may mimic the aforementioned phenomenon in humans whereby an episode of prolonged seizure (febrile or nonfebrile) between the ages of 6 months and 7 years may produce hippocampal sclerosis, which in turn may be associated with spontaneous complex partial seizures in later life.[15-18]

The mechanism of neuronal damage during prolonged status epilepticus may be related to reduced inhibition through the γ-aminobutyric acid system, enhanced glutaminergic excitatory transmission, and calcium-mediated cell damage.[10,25,39,40,44]

Initial Treatment of Patients in Generalized Tonic-Clonic Status Epilepticus

From the various pathophysiologic mechanisms described earlier, it should now be clear that time is of the essence in the treatment of status epilepticus. Thus, it seems desirable that every facility should have a predetermined protocol for the treatment of status epilepticus that includes a time frame (Table 3). First, patients should be assessed for signs of cardiorespiratory compromise, hyperthermia, focal neurologic signs, head trauma, or CNS infection, and their seizures should be observed to ascertain that they are in status epilepticus. Baseline laboratory studies should be done, including antiepileptic drug levels, serum levels of electrolytes, glucose, calcium, magnesium, creatinine, and urea nitrogen, a complete blood count, metabolic screen, and drug and toxicology screens. Arterial blood gases should be measured to assess baseline oxygen saturation and pH. If needed, an oral airway should be inserted and oxygen administered. An intravenous (IV) infusion should be started with a saline solution. Thiamine, 100 mg IV, should be administered, and this should be followed by 50 ml of a 50% glucose solution by IV push. Cardiopulmonary resuscitating equipment should always be at the bedside of a patient in status epilepticus in case of a sudden deterioration.

Drug Therapy for Status Epilepticus

Common Drug Regimens

Although much has been written about status epilepticus and its treatment over the years, few well-controlled, prospective, randomized drug trials have been undertaken of this condition.[45-47] The three most commonly used drug regimens for the treatment of status epilepticus include the use of phenytoin alone, a benzodiazepine plus phenytoin, and phenobarbital alone. Each of these will be reviewed briefly and a specific protocol recommended.

TABLE 3.—*Treatment of Status Epilepticus*

Time Frame	*Procedure*
0-5 min	Assess cardiorespiratory function, take history, and perform neurologic and physical examination; draw blood specimens for antiepileptic drug levels, glucose, BUN, creatinine, calcium, magnesium, electrolytes, complete blood count, metabolic screen, drug screen, and arterial blood gases; insert oral airway and administer oxygen if needed
6-9 min	Start IV infusion with saline solution; administer 25 grams glucose and B vitamins
10-45 min	Infuse lorazepam, 0.1 mg/kg (4 to 8 mg), at <2 mg/min
	Also begin infusion of phenytoin, 20 mg/kg, at a rate of 25 mg/min; this may take 20 to 40 min; monitor ECG, respirations, and blood pressure
	If seizures persist, give additional phenytoin, 5 mg/kg, at same rate, and, if needed, another 5 mg/kg until a maximum of 30 mg/kg has been given
46-60 min	If seizures persist, intubate and give phenobarbital, 20 mg/kg, at <100 mg/min IV
1 hour	If seizures persist, pentobarbital coma or general anesthesia should be started

BUN = blood urea nitrogen, ECG = electrocardiogram, IV = intravenous

Phenytoin (Dilantin) only. The main advantages of using phenytoin in the treatment of status epilepticus are its proven effectiveness in controlling seizures, its relatively long half-life, and its lack of significant CNS depression. Disadvantages include its cardiovascular side effects if given too rapidly (arrhythmia, hypotension), the time required to give an average loading dose (20 to 40 minutes), its relative ineffectiveness in suppressing focal seizures, the possibility of local tissue irritation, and its tendency to crystallize in the IV line. When using phenytoin, blood pressure and the electrocardiogram (ECG) should be monitored and the drug must be given in a saline solution. Phenytoin must *not* be given in a glucose-containing IV solution.[48-52]

Benzodiazepine plus phenytoin. The main advantage of combination therapy using a benzodiazepine plus phenytoin is that the seizures may be rapidly controlled with the benzodiazepine, followed by the use of phenytoin for its sustained antiepileptic action. Therefore, a benzodiazepine is used to offset the time required to infuse an adequate loading dose of phenytoin. The disadvantage of this combination is that two drugs are used instead of one, which may lead to drug interactions that could result in respiratory depression and hypotension. During the use of a benzodiazepine with phenytoin, blood pressure, respirations, and the ECG should be monitored closely.

In the United States, two benzodiazepine preparations are commonly used in the treatment of status epilepticus. Diazepam became popular in the 1960s because of its rapid onset of anticonvulsant action. Although it acts rapidly, diazepam is quickly redistributed out of the brain and into fat stores.[45,53] Therefore, its antiepileptic action lasts only about 20 to 30 minutes, and repeated doses of diazepam are often necessary if seizures are to remain controlled. This can severely hamper the subsequent treatment of the seizures if status epilepticus is not easily controlled and recurs after the drug redistributes. Lorazepam also has a fairly rapid onset of action but has a much longer effective duration of action, thereby eliminating the need for repeated doses. In fact, some studies indicate that lorazepam may terminate status epilepticus for as long as 12 to 24 hours, allowing more time to institute definitive antiepileptic drug therapy.[46,54,55] For these reasons, if a benzodiazepine is used, lorazepam is probably preferred over diazepam.

Great care must be exercised if a benzodiazepine (especially repeated doses of diazepam) and phenobarbital are used sequentially in the treatment of status epilepticus. Their hypotensive and respiratory depressant actions synergize and may cause abrupt and serious side effects. Therefore, unless absolutely necessary, it is generally recommended that either one or the other of these medications be used without combining them.[47,54,56-61]

Phenobarbital only. The advantages of phenobarbital include its long half-life, its effectiveness in both generalized and focal seizures, and the fact that it can be administered more rapidly than phenytoin. The main disadvantages of phenobarbital include its tendency to depress a patient's level of consciousness, to contribute to respiratory depression, and to interact with benzodiazepines. During the administration of phenobarbital, the patient's blood pressure and respiratory rate should be continuously monitored.[47,52]

Recommended Drug Protocol

Many comprehensive epilepsy centers recommend some variation of the following protocol (Table 3)[5,29,62,63] (also, A. L. Sherwin, MD, Montreal Neurological Institute, oral communication, January 1991). After the initial assessment of a patient and the placement of an IV line, administer lorazepam, 0.1 mg per kg (4 to 8 mg), at a rate of less than 2 mg per minute. Blood pressure, respirations, and ECG should be monitored during this infusion.

If the patient's seizures do not stop with the administration of lorazepam, begin infusing phenytoin, 20 mg per kg, at a rate of 25 mg per minute. This infusion rate will require 20 to 40 minutes to complete but usually will avoid cardiovascular side effects such as hypotension and arrhythmias.[51]

If the seizures persist, an additional phenytoin dose of 5 mg per kg may be administered at the same rate (25 mg per minute). If this is not effective, an additional 5 mg per kg can be infused, bringing the total phenytoin dose to a maximum of 30 mg per kg.[29,54]

If seizures continue, even more aggressive therapy is indicated. Before this is initiated, an endotracheal tube should be inserted, and the patient will obviously need to be under close medical supervision by an intensive care specialist as well as a neurologist. After intubation, administer phenobarbital, 20 mg per kg, at a rate of less than 100 mg per minute.[29,54]

If seizures persist, pentobarbital coma or general anesthesia should be initiated because at this point the patient has been in status epilepticus for at least an hour. The risk of prolonged or permanent brain damage is present if status epilepticus is allowed to continue for longer than 60 minutes.[5,29,54,64-69] Pentobarbital coma must be conducted in an intensive care unit with the patient intubated, mechanically

ventilated, and maintained under continuous cardiovascular, respiratory, and EEG monitoring. A loading dose of pentobarbital (5 to 10 mg per kg IV) is given slowly to induce a "burst-suppression" EEG pattern. This EEG pattern is maintained with a continuous IV infusion of pentobarbital (1 to 5 mg per kg per hour). The infusion is slowed or terminated every 2 to 12 hours and reinstated if seizures recur. Such treatment may be required for days to weeks in refractory cases.[5,29,64-69]

Future Developments in the Treatment of Status Epilepticus

To determine the most appropriate therapeutic regimen for the treatment of status epilepticus, a large, prospective, double-blind, multicenter cooperative study was initiated by the Division of Veterans Affairs in June of 1990. This study will include more than 1,100 patients with generalized tonic-clonic status epilepticus and is scheduled to be completed in 1993. Four regimens are being compared. These include phenytoin, 18 mg per kg; diazepam, 0.15 mg per kg, followed by phenytoin, 18 mg per kg; lorazepam, 0.1 mg per kg; and phenobarbital, 15 mg per kg. By 1993, we should have additional information concerning the best treatment regimen for this condition.[70]

It is hoped that more specific therapy for status epilepticus can be devised in the future. Such medications may include antagonists of excitatory amino acid neurotransmitters such as glutamate, specific calcium channel blockers, and agonists of inhibitory neurotransmitters such as γ-aminobutyric acid.[71] In addition, a phenytoin prodrug is under investigation in an attempt to circumvent some of the difficulties experienced with the use of phenytoin as presently formulated.[72,73] Investigations using an IV preparation of valproic acid are also under way.[74,75] Therefore, it can be expected that within the next decade we will not only have established the best drug regimen for the treatment of status epilepticus with currently available medications, but we will also have discovered novel and specific medications to use in the treatment of this serious malady.

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Epitomes

Important Advances in Clinical Medicine

Urology

The Scientific Board of the California Medical Association presents the following inventory of items of progress in urology. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome, and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, researchers, or scholars to stay abreast of these items of progress in urology that have recently achieved a substantial degree of authoritative acceptance, whether in their own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Urology of the California Medical Association, and the summaries were prepared under its direction.

Reprint requests to Division of Scientific and Educational Activities,
California Medical Association, PO Box 7690, San Francisco, CA 94120-7690

Prostate-Specific Antigen

PROSTATE-SPECIFIC ANTIGEN (PSA) is a serine protease normally produced by prostatic epithelial cells and present in high concentrations in prostatic secretions. In normal men, it is present in the serum in minute quantities. Most pathologic states involving the prostate, however, have the potential to cause marked elevations of serum PSA concentrations. Bacterial prostatitis, benign prostatic hyperplasia, and prostate cancer all elevate serum PSA levels to varying degrees. Prostate-specific antigen has found the most widespread clinical application in the evaluation and management of patients with prostate cancer.

Prostate-specific antigen has displaced prostatic acid phosphatase as the preeminent tumor marker for prostatic adenocarcinoma. The combination of several key features makes PSA unique among known tumor markers. It is remarkably sensitive to the presence of prostate cancer. Serum PSA values are elevated in more than 95% of palpable cancers, including small palpable nodules (stage B1 lesions). Serum levels of PSA are remarkably proportional to both clinical stage and pathologic stage found at radical prostatectomy. In fact, careful pathologic studies show that serum PSA is directly proportional to the volume of prostate cancer. Because the clinical and pathologic stages of prostate cancer, perhaps more so than any other malignant neoplasm studied, also appear to be a direct function of tumor volume, PSA has proved a useful adjunct in staging. In untreated patients with prostate cancer who have undergone careful pathologic staging, it is almost unheard of to find regional lymph node metastases when serum PSA levels are less than 10 μg per liter by the Yang assay (about 5.5 μg per liter by the more commonly used Hybritech assay). In untreated patients with serum PSA levels above 75 μg per liter by the Yang assay (50 μg per liter by the Hybritech assay), nearly two thirds have lymph node metastases, three quarters have seminal vesical invasion by cancer, more than four fifths will have extensive tumor volume and surgical margin involvement, and all will have high-grade lesions. Unfortunately, as with any biologic system—especially a deranged biologic system, which cancer is by definition—exceptional patients with high-volume prostate cancers and high serum PSA values may have organ-confined disease, and patients with low-volume tumors and low PSA values may have early metastases. Also, because PSA is nonspecific for prostate cancer, serum levels may be elevated by coexistent prostatic disease, including bacterial prostatitis and benign prostatic hyperplasia. Therefore, although a valuable adjunct to our current clinical staging of patients with prostate cancer, measuring the PSA level does not eliminate the need for careful clinical assessment, including a digital rectal examination, technetium bone scans, and appropriate radiographic studies.

Prostate-specific antigen provides an excellent objective measure in observing patients with prostate cancer. Serum PSA levels rise over time and correlate with clinical progression of the disease process in untreated patients with prostate cancer. Moreover, exponential increases in serum PSA levels usually precede clinical disease progression and may allow preemptive treatment planning. Any successful treatment of prostate cancer dramatically affects serum PSA levels. In patients responding to androgen ablation, serum PSA levels fall precipitously, with nadir values typically reached by 3 to 6 months. After radiotherapy, PSA values fall in a similar manner but with a more prolonged time course, and nadir values are reached at 12 to 18 months. Patients for whom either androgen ablation or radiotherapy fails also behave similarly, with exponentially rising serum PSA values usually preceding symptomatic clinical recurrence or progression.

One clearly defined use for PSA is in observing patients after radical prostatectomy. These patients, if their cancer and prostate are completely surgically excised, should have no PSA in their serum. Given the serum half-life of the PSA molecule (between 2.2 and 3.2 days), most patients should have zero serum PSA values by three weeks, and all should be zero by six weeks. The persistence or recurrence of PSA in the serum after radical prostatectomy accurately predicts residual or metastatic cancer and usually presages clinical disease recurrence by many months or years.

JOHN N KABALIN, MD
Palo Alto, California

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BCG Vaccine in Urinary Bladder Cancer

NEARLY TWO THIRDS of all urinary bladder cancers are confined to the urothelial surface or lamina propria when they are first recognized. Two types of transitional cell carcinoma can be identified. The first is a papillary growth and is usually treatable by transurethral resection or laser phototherapy. The recurrence rate for these carcinomas varies from 20% to 80% depending on the grade of the tumor and whether it has penetrated the basement membrane and is growing into the lamina propria.

The need to diminish the rate of recurrence of these tumors has led to the use of a number of agents that can be instilled directly into the urinary bladder. One of the most effective is bacillus Calmette-Guérin (BCG), an attenuated tuberculosis vaccine containing live tubercle bacilli. When BCG is repeatedly instilled into the bladder, an inflammatory and immunologic reaction occurs. This reaction has the benefit of reducing the recurrence rate to the range of 15% to 20%. Candidates for this therapy are patients who have previously had tumors, those with grade 2 or 3 tumors, those with tumors extending into the lamina propria, and patients with multiple tumors. One suggested protocol has patients receiving six instillations, usually weekly, followed by monthly instillations for a year.

The second type of tumor is carcinoma in situ, which grows laterally along the surface of the urothelium. Before BCG, the only therapy for this cancer was cystectomy. Patients with carcinoma in situ usually receive 12 instillations of BCG, which has a 70% probability of eradicating the disease.

Thus, BCG is considered the first line of therapy for decreasing the probability of a tumor recurrence and eliminating carcinoma in situ. It is currently the most effective agent for accomplishing these goals. This success can be accompanied by adverse reactions, however. Localized side effects reflect the inflammatory reaction in the bladder and may produce symptoms of frequency, urgency, dysuria, and hematuria. These symptoms are usually mild and last only a few days. In a few patients a systemic reaction occurs. This begins as a "flulike" illness with a low-grade fever and malaise lasting 48 to 72 hours. When the reaction is more severe, patients can be treated with isoniazid, which minimizes these symptoms but does not abrogate the anticancer effect. Rarely, sepsis can develop that requires vigorous antituberculosis therapy. When used in appropriate circumstances and with careful observation of the patient, intravesical BCG therapy is safe and effective for many patients with urinary bladder cancer.

Those who mix and administer the BCG solutions are not at risk of harm as long as a sterile technique and safe work practices are observed and all of the materials are disposed of in an appropriate manner.

STANLEY A. BROSMAN, MD
Santa Monica, California

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Medical Treatment of Benign Prostatic Hyperplasia

FOR SEVERAL DECADES, the preferred treatment of benign prostatic hyperplasia has been transurethral or open prostatectomy. Recent advances in our understanding of lower urinary tract physiology and the growth and development of the prostate gland have resulted in new medical therapies for some men with this disorder.

Based on the finding of higher concentrations of α_1-adrenergic receptors at the bladder neck, prostatic capsule, and prostatic substance, agents that block such receptors can be used. Selective α_1-blocking drugs, such as prazosin hydrochloride and terazosin hydrochloride, can "relax" the smooth muscle in these areas, allowing the urinary bladder to work more efficiently. α-Blockers do not shrink the prostate but instead are active on the dynamic component of prostatic enlargement. The major side effect of these drugs, which are commonly used for the control of hypertension, is orthostatic hypotension. The drug dose must be carefully titrated against the patient's response and side effects.

Efforts to block or interfere with the androgen stimulation of benign prostatic hyperplasia have been effective in shrinking the prostate gland by about 30% to 50%. In some men with mechanical obstruction, this modest reduction in size may be sufficient to alleviate symptoms and thus reduce the necessity for an operation. Endocrine manipulation can be carried out in several ways: blocking the effect of androgens (mainly dihydrotestosterone) with antiandrogens, such as flutamide; decreasing the testicular output of androgens using luteinizing hormone-releasing hormone (LHRH)-agonists, such as leuprolide acetate and goserelin; and using an inhibitor of 5-α-reductase, such as finasteride, that thereby reduces the formation of dihydrotestosterone.

Side effects are specific for each class of endocrine therapy. The antiandrogen may cause gynecomastia and diarrhea. The use of LHRH-agonists is associated with a decrease in libido, impotence, and hot flashes. Inhibitors of 5-α-reductase are relatively nontoxic, with impotence the only side effect reported.

The use of combinations of α-blocking agents and endocrine manipulation is currently under study. Clinical trials employing medical therapy for benign prostatic hyperplasia have emphasized the need for better response indicators. These include subjective measures, such as symptom scores and global assessment (quality of life and interference in daily activities), and objective ones, such as measuring voiding pressure, urinary flow rate, and residual urine.

Because this disorder probably begins 20 or more years before clinical symptoms and signs are evident, medical therapy may be effective only in those men in whom changes of decompensation, such as bladder diverticula and hydronephrosis, have not yet developed.

JOSEPH D. SCHMIDT, MD
San Diego, California

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Screening for Prostate Cancer

THE 1990 CANCER STATISTICS reveal that prostate cancer is now tied with lung cancer as the most common cancer in men. It is expected that more than 30,000 men will die of prostate cancer this year. Potentially curative treatments are available for disease localized to the prostate gland, yet less than half of patients have localized disease at the time of diagnosis.

In the past, the early detection of prostate cancer has relied solely on the digital rectal examination. Current guidelines of the American Cancer Society recommend yearly digital rectal examinations for men older than 40 years. Several studies have clearly shown the shortcomings of the digital rectal examination as a diagnostic technique, however. It is highly subjective and has low sensitivity and specificity, with a positive predictive value between 17% and 30%. Earlier searches for more objective alternatives to this examination turned to the measurement of prostatic acid phosphatase levels. After years of study, prostatic acid phosphatase remains ineffective as a diagnostic test for organ-confined disease and is used almost exclusively for monitoring metastatic prostate cancer. More recent efforts at improving the early diagnosis of prostate cancer have focused on transrectal ultrasonography of the prostate and the measurement of serum levels of prostate-specific antigen (PSA).

Transrectal ultrasonography of the prostate has grown widely in popularity in recent years. Continued progress in equipment technology and scientific assessment of its capabilities have resulted in an effective tool when used within its limitations. Transrectal ultrasonography is incapable of differentiating malignant from benign lesions of the prostate. It should not be used as a screening method in men with otherwise benign prostates by digital rectal examinations and PSA measurements because of poor sensitivity, specificity, and poor positive predictive value. In addition, it would not be cost-effective on a mass population screening level. It has, however, proved to be a useful adjunct when evaluating patients with other high-risk findings such as abnormal findings on a rectal examination or elevated PSA levels. It is also highly effective in guiding histologic examination of specimens during prostate needle biopsies. We currently recommend that transrectal ultrasonography of the prostate be used primarily by a trained urologist for patients with indications for prostate biopsy.

Since its discovery in 1979, prostate-specific antigen has shown its widening usefulness in the management of patients with prostate cancer. It is secreted only by prostatic epithelial cells and is not specific for prostate cancer. Because PSA is produced by both benign and malignant prostate cells, it was originally thought that this would limit, if not completely exclude, its use as a diagnostic tool for prostate cancer. Further evidence, however, shows a substantial differential rate of the production. Prostate cancer cells apparently produce about ten times more PSA per gram of tissue than benign prostatic cells. Thus, even small volumes of prostate cancer can raise serum levels of PSA significantly more than greater volumes of benign prostatic hyperplasia. Recently reported data support the value of the measurement of this antigen (using the Hybritech assay) as a screening test for prostate cancer. Positive predictive values of about 65% have been reported for patients with serum PSA levels of 10 μg per liter or higher and 25% for levels between 4.0 and 9.9 μg per liter. The advantages of PSA determination in screening are that it is objective, quantitative, and more acceptable to patients than the embarrassment and discomfort of a digital rectal examination. In addition, the combination of a PSA measurement and a rectal examination can provide an even greater level of accuracy. In the future, it may be confidently recommended that all men obtain routine PSA determinations as a screen for prostate cancer, but insufficient data are available at this time for such a conclusion.

Several thoughtful investigators have questioned the basic value of prostate cancer screening, citing insufficient evidence that mortality or quality of life will be affected significantly, in addition to causing some patients' unnecessary worry and unneeded treatment. These aspects clearly need to be considered until long-term studies are completed that address these important points. At present, however, patients who, rightly or wrongly, are apprehensive about prostate cancer must be treated. It is difficult to hold back from them a potentially important diagnostic test. Unfortunately, medical judgment is being driven by the ever-increasing onslaught of new, untested technology.

The digital rectal examination, despite its limitations, continues to be the simplest and most cost-effective method of detecting prostate cancer. The use of transrectal ultrasonography for screening the prostate should be discouraged because of its inherent inability to discriminate between benign and malignant disease and its considerable cost. Insufficient data are available to recommend the routine screening of all men with prostate-specific antigen, but its use as an adjunct in the detection of prostate cancer in men with other risk factors is clear.

MICHAEL T. MAC FARLANE, MD
Los Angeles, California

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Laparoscopy in Urology

LAPAROSCOPY, LONG A MAINSTAY of gynecologic diagnosis and therapy, has received much recent publicity regarding applications in abdominal general surgery and in urology. Urologists have always been trained as endoscopic surgeons, and laparoscopic surgery is a logical extension of their therapeutic options. Laparoscopic procedures must be compared with the standard incisional approach by two criteria: the procedure should be of substantially equivalent or superior efficacy, and it should have similar or less morbidity. In general, the advantage of the laparoscopic technique lies in decreased morbidity. Hospital stays tend to be shorter, if required at all, and the return to usual preoperative activities, including work, is usually faster after laparoscopic procedures than after standard open procedures.

The evaluation and possible treatment of nonpalpable undescended testes most clearly meet the criteria of good efficacy and decreased morbidity. A laparoscopic demonstration of blind-ending gonadal vessels eliminates the need for surgical exploration in some of these children, and, in certain other cases, laparoscopy allows a preliminary manipulation of testicular blood flow, which may improve the likelihood of

successful surgical orchiopexy at a later date. Laparoscopy in the diagnosis and treatment of nonpalpable undescended testes should not be considered a necessity, but it can be useful when done by a surgeon proficient in the technique.

Laparoscopic pelvic lymph node dissection to stage urologic malignancy and laparoscopic varicocele ligation have also been reported with good results and appear to be as effective, with equal or less morbidity, as open surgical procedures. The laparoscopic approach is particularly attractive in the staging of prostate and perhaps bladder cancer, as the documentation of metastatic disease by laparoscopy may spare a patient an extensive surgical exploration. Once again, in these indications, laparoscopy should be viewed as an option, possibly beneficial in certain selected patient populations when done by an experienced practitioner, and not as a requirement in the care of these diseases.

Other procedures are now being described in reports from clinical practice or animal laboratories. For example, human nephrectomy has already been performed laparoscopically. Although theoretically there are few limits to the extent to which this technology can be advanced, each potential "advance" must be compared with standard therapy to determine its clinical usefulness, if any.

GEORGE DANIELS, JR, MD
Stanford, California

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Extracorporeal Shock-Wave Lithotripsy With Minimal or No Anesthesia

EXTRACORPOREAL SHOCK-WAVE LITHOTRIPSY (ESWL) has revolutionized the treatment of patients with nephrolithiasis and ranks as one of the great accomplishments of the past decade in medicine. Since its clinical introduction in Germany in 1980 and in the United States in 1984, ESWL has become the procedure of choice for most patients with nephrolithiasis requiring surgical treatment. With literally hundreds of thousands of patients treated worldwide to date, its safety record also compares favorably with any other surgical procedure. Today, major efforts are directed toward improving the ease of ESWL treatment for both patients and physicians, with special emphasis on decreasing anesthesia requirements.

Extracorporeal shock-wave lithotripsy procedures with the German-made Dornier HM3 machine, the original or "first-generation" lithotriptor that remains in popular use, nearly always require either general or regional (spinal or epidural) anesthesia. This machine also requires subtotal immersion of the patient within a water bath. Newer second-generation ESWL machines marketed today have almost universally eliminated the need for patient immersion. They also have much-reduced anesthesia requirements. The reduced anesthesia requirements promise a further reduction in the already minimal morbidity associated with ESWL. This reduced anesthesia requirement, however, has been achieved only at the expense of some decrement in machine power. The original Dornier HM3 lithotriptor remains the "gold standard" device in terms of its proven ability to produce adequate stone fragmentation over a wide range of stone size and composition, using the fewest number of shock waves.

Among the second-generation lithotriptors, a variably lessened efficiency in stone fragmentation is weighed against variably lessened anesthesia requirements. At one end of the spectrum of the second-generation lithotriptors are the piezoelectric devices, which produce the least patient discomfort during treatment, allowing many patients to be treated with no anesthesia. Electromagnetic devices now available allow most patients to be treated with only intravenous sedation. Gains in anesthesia requirements, however, are offset to some degree by the need for many more shock waves for each stone and often many treatment sessions. At the other end of the spectrum of second-generation lithotriptors are machines that still use a spark-gap electrode power source, such as the United States-made Medstone STS machine. These machines more closely approximate the fragmentation results and retreatment rates achievable with the original HM3 machine, while still allowing most patients to be treated with only light intravenous sedation.

All of the new second-generation lithotriptors have in common a notable reduction in anesthesia requirement. With their use, patients are awake and comfortable during the treatment of their kidney stones. Patients can be ambulatory and resume normal oral intake immediately after the completion of ESWL and thus be treated as outpatients. Many patients who might otherwise have avoided the treatment of their kidney stones find ESWL much more attractive with such a regimen. Perhaps even more important, the ability to deliver treatment with minimal or no anesthesia extends the ready applicability of ESWL to that group of patients with nephrolithiasis and severe coexisting medical problems in whom the risks of anesthesia might be prohibitive.

JOHN N. KABALIN, MD
Palo Alto, California

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Male Infertility Update

THERE HAVE BEEN SEVERAL advances recently in the field of male infertility, including improvements in vasovasostomy and vasoepididymostomy, the micromanipulation of human gametes, the ease of measuring antisperm antibodies, and further tests of the fertilizing capacity of sperm including the sperm penetration assay (or hamster test).

About 500,000 men a year undergo a vasectomy in the United States for permanent sterilization. With the increase in the divorce and remarriage rates, many of these men wish to have their vasectomies reversed. Beginning in the mid-1970s, the operating microscope came into wide use to aid in the anastomosis of vasa deferens. It soon became apparent that more was needed than simply reconnecting the newly severed ends. At times, the fluid seen from the upstream portion of the vas was inspissated and contained no sperm. With the use of the operating microscope, attempts were then made to reconnect the vas to a proximal area, such as the

epididymis. The results have been encouraging. If sperm are found at the proximal portion of the vas during the operation and if the distal lumen is patent, there is a 90% chance of obtaining spermatozoa in the ejaculate and a 75% pregnancy rate in a year. If no sperm are seen and the fluid is abundant and clear, there is about a 50% chance of a pregnancy in a year. If there are no sperm and the fluid is poor, the chances for pregnancy decrease to about 1%, and a vasoepididymostomy may be indicated. This can only be accomplished using microsurgical techniques. Frequently the tubules proximal to the area of obstruction are dilated and can be easily teased away from the surrounding structures and opened. A vasoepididymostomy can be done when sperm are present, with a fertility rate of about 30% if the vas is connected to the tail of the epididymis. If the vas is connected to the head of the epididymis, a 10% pregnancy rate is reported.

A recently developed test of sperm function is the sperm penetration assay. This assay, which is carried out in several centers around the United States, uses specially prepared hamster eggs incubated with treated sperm to assess the capability of sperm to penetrate the eggs. It was found that the zona pellucida of the hamster egg guards against non-hamster species sperm, the species-specific discriminator. When this is removed, motile sperm from any species can penetrate the hamster egg if the sperm are properly capacitated. This has been a helpful test at in vitro fertilization centers to explain the inability of certain sperm to penetrate human eggs. There is a good correlation between a good score on the sperm penetration assay and the success of an in vitro fertilization procedure. This test has evolved so that patients with an extremely low sperm count can still be tested using small, specially prepared incubation chambers.

Patients who have a congenital absence of the vas or whose distal portion of the vas is unacceptable for vasectomy reversal can now father children. The patient and his partner undergo a simultaneous aspiration of oocytes from her and spermatozoa from his epididymis. Epididymal aspiration techniques are currently being used in large centers throughout the country for fertilization of these otherwise infertile couples. Briefly, the woman is brought into an in vitro fertilization cycle. On the day of oocyte retrieval, the man undergoes a surgical procedure. At this time, the epididymis is exposed, a single epididymal tubule is teased away from the rest of the epididymis and, using the operating microscope, is incised. The contents are gently aspirated using a special capillary tube. The motile sperm are then processed and used for an in vitro fertilization cycle. Frequently the fertilized ovum is replaced in the fallopian tube at the zygote stage (zygote intrafallopian tube transfer.) If the pre-embryo develops and implants, a pregnancy occurs. Several pregnancies have been reported recently. This has been a recent improvement in our ability to handle patients with congenital absence of the vas and requires special training in centers.

PHILIP WISE, MD
San Diego, California

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Orange

Alerts, Notices, and Case Reports

Fatal Salicylate Toxicity From Bismuth Subsalicylate

STEVEN J. SAINSBURY, MD
Templeton, California

FATAL SALICYLATE INGESTION usually results from concentrated formulations of salicylates found in analgesics, cold and sinus medications, and aspirin-containing topical compounds.

I describe a case of salicylate toxicity leading to death secondary to the abuse of Pepto-Bismol, whose active and toxic ingredient is bismuth subsalicylate.

Report of a Case

The patient, an 82-year-old previously healthy woman, presented to the Riverside (California) Community Hospital Emergency Department with an altered level of consciousness, according to her son with whom she was living. In the previous 24 hours, she had exhibited slurred speech, lethargy, and a decreased oral intake. Her son also reported that for several days she had complained of an exacerbation of her chronic abdominal pain. As a result, she had been ingesting large amounts of Pepto-Bismol tablets daily, including 66 tablets in the 24 hours before admission. There was no history of nausea or vomiting. Stools had been watery and black for several days.

Her medical history was significant for chronic abdominal pain that remained undiagnosed despite extensive evaluations in the past. She had not seen a physician in several years. Current medications included only Pepto-Bismol. She was allergic to codeine.

On her initial examination, this frail, small-of-stature elderly woman was confused and lethargic. Her supine blood pressure was 118/70 mm of mercury with a pulse rate of 70 per minute, a respiratory rate of 20, and a temperature of 37°C (98.6°F); she weighed 36 kg (79 lb). Her skin was warm and dry with tenting. Mucous membranes were dry. Auscultation of her lungs revealed rales at the left base. The abdomen displayed no palpable mass, rebound, guarding, or organomegaly. On rectal examination, the stool was dark brown and guaiac-negative. On neurologic examination, she was disoriented in all spheres and lethargic.

The following laboratory values were obtained: hemoglobin 111 grams per liter (11.1 grams per dl); hematocrit 0.32; leukocyte count 11.2×10^9 per liter (11,200 per μl), with 0.87 neutrophils, 0.06 bands, and 0.06 lymphocytes; sodium 143, potassium 3.5, chloride 108, and carbon dioxide content 16 mmol per liter; blood urea nitrogen 1.0 mmol per liter (28 mg per dl); creatinine 97 μmol per liter (1.1 mg per dl); prothrombin time 15.5 seconds (control 11 to 13); partial prothrombin time 30.2 seconds (control 20 to 30); and glucose level 6.0 mmol per liter (108 mg per dl). Arterial blood gas determinations with the patient receiving 2 liters of oxygen showed a pH of 7.55, a P_{CO_2} of 14 mm of mercury, and a P_{O_2} of 160 mm of mercury, consistent with a mixed respiratory alkalosis and metabolic acidosis. A salicylate level was 46 mg per dl.

Other studies included a normal electrocardiogram and upright chest radiograph. A plain film of the abdomen revealed pronounced densities in the bowel, consistent with "barium or some other radio-opaque substance," according to the radiologist's interpretation (Figure 1). Computed tomography of the head showed diffuse cortical atrophy.

The patient was admitted to the care of her family practitioner with a diagnosis of dehydration, encephalopathy, and salicylate toxicity due to Pepto-Bismol abuse. Despite hydration and urinary alkalinization over the next two days, her condition continued to deteriorate, and she had progressively lower hematocrits, higher leukocyte counts, and steady salicylate levels and anion gaps. A gastroscopy revealed mild generalized intestinal inflammation but no focal bleeding. Three days after admission, her hematocrit was 0.19, a salicylate level was 20 mg per dl, and the anion gap was 24. She died of pulmonary edema on the same day.

Discussion

As a result of safety packaging and the rise of acetaminophen use as an antipyretic in children, there has been a dramatic decrease in the incidence of salicylate deaths in children over the past several years.[1] Yet, aspirin remains as a relatively common source of poisoning in adults. Integrated into more than 200 different formulations (probably more than any other drug), salicylates are commonly overlooked by patients and physicians alike as a source of potential toxicity (Table 1).[2-4]

Figure 1.—A plain film of the abdomen shows pronounced densities in the bowel.

(Sainsbury SJ: Fatal salicylate toxicity from bismuth subsalicylate. West J Med 1991 Dec; 155:637-639)

From the Emergency Department, Twin Cities Community Hospital, Templeton, California.

Reprint requests to Steven J. Sainsbury, MD, Emergency Department, Twin Cities Community Hospital, 1100 Las Tablas, Templeton, CA 93465.

TABLE 1.—*Common Sources of Salicylates*

Selected Formulations (Manufacturer)	*Generic and Chemical Name*
Prescription	
Darvon Compound (Eli Lilly and Co)	Propoxyphene HCl, aspirin, and caffeine
Empirin with Codeine (Burroughs Wellcome)	Aspirin and codeine phosphate
Fiorinal (Sandoz)	Butalbital, aspirin, and caffeine
Percodan (DuPont)	Oxycodone HCl, oxycodone terephthalate, and aspirin
Over-the-Counter	
Aspirin tablets and suppositories (numerous preparations)	--
Alka-Seltzer (Miles Inc)	Aspirin, sodium bicarbonate, citric acid, sodium citrate, and sodium salicylate
Ascriptin (Rhone-Poulenc Rorer)	Aspirin, magnesium hydroxide, dried aluminum hydroxide gel, and calcium carbonate
Aspercreme (Thompson Medical)	Topical cream containing trolamine salicylate
Ben-Gay External Analgesic (Pfizer)	Topical cream containing methyl salicylate and menthol
Bufferin (Bristol-Myers)	Aspirin, calcium carbonate, magnesium oxide, and magnesium carbonate
Cope (Glenbrook)	Aspirin and caffeine
Dristan (Whitehall)	Phenylephrine HCl, chlorpheniramine maleate, and acetaminophen
Ecotrin (SmithKline Beecham)	Enteric-coated aspirin
Excedrin (Bristol-Myers)	Acetaminophen, aspirin, and caffeine
Midol (Glenbrook)	Acetaminophen, pamabrom, and pyrilamine maleate
Oil of wintergreen	Methyl salicylate
Pepto-Bismol (Procter & Gamble)	Bismuth subsalicylate
Sine-Aid (McNeil)	Acetaminophen and pseudoephedrine HCl
Triaminicin (Sandoz)	Phenylpropanalamine HCl and chlorpheniramine maleate
Vanquish (Glenbrook)	Aspirin, acetaminophen, caffeine, dried aluminum hydroxide gel, and magnesium hydroxide

HCl = hydrochloride

The elderly in particular are at high risk for both accidental and chronic salicylate poisoning.[5] Presenting frequently with an altered sensorium, they can prompt a fruitless search for a primary neurologic cause, delaying critical treatment of their toxic syndrome. Even when salicylates are identified as the source of a patient's illness, determining the degree of toxicity is difficult. The usefulness of the Done nomogram is currently unclear, and it is certainly invalid in cases of chronic toxicity, with the use of enteric-coated preparations, and when there is delayed gastric emptying or salicylate concretions.[4,6]

Salicylates uncouple oxidative phosphorylation and inhibit dehydrogenases and aminotransferases, leading to a rise in organic anions and metabolic acidosis. They also stimulate the respiratory system, resulting in hyperventilation and respiratory alkalosis. This in turn leads to the renal excretion of bicarbonate and potassium. Larger doses can depress respirations. Hypothrombinemia and platelet dysfunction are common complications of salicylate toxicity, producing prolonged bleeding times. Other effects are diaphoresis and hyperthermia, each worsening dehydration.[1,4]

The clinical features of salicylate toxicity are hyperpnea, confusion, lethargy, tinnitus, vomiting, and abdominal pain. Signs include fever (particularly in children), diaphoresis, dehydration, and hyperventilation. Coma indicates a poor prognosis.[1,4,7]

The treatment of salicylate poisoning is challenging. Despite their dehydration, many patients are predisposed to noncardiogenic pulmonary edema. Forced alkaline diuresis, the cornerstone of emergency department therapy, can worsen this condition. Excessive bicarbonate administration to increase the renal excretion of salicylates or to correct the salicylate-induced metabolic acidosis can lead to equally dangerous alkalinemia. Hemodialysis can be effective in eliminating salicylates, but its use should be reserved for severely poisoned patients.[1,4,8]

The patient in this report had most of the classic features of salicylate poisoning. She presented with dehydration and central nervous system dysfunction. Examination revealed acid-base and clotting disorders, with progressive central nervous system depression, anemia, pulmonary edema, and eventually death. Because of long-term salicylate use, in the form of enteric-coated tablets, the salicylate level underestimated both the degree and likelihood of the progression of toxicity.

What is atypical is the source of the salicylate: Pepto-Bismol tablets, each of which contains 262 mg of bismuth subsalicylate and 102 mg of available salicylate.[9] The recommended dosing schedule—2 tablets orally four times a day—would deliver 11.6 mg of salicylate per kilogram per day in a 70-kg adult, less than 3 mg per kg per dose. In this case study, the ingestion of 66 tablets by a 36-kg patient resulted in a dose of 187 mg per kg—taken in conjunction with probable underlying long-term salicylate abuse. Although mentioned frequently in the literature as a source of absorbable salicylate, Pepto-Bismol use has not been reported in an actual death from salicylate toxicity.[9-11]

The key to effective intervention in salicylate toxicity remains the prompt recognition of its existence, whether it be accidental, suicidal, or iatrogenic.

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Ciguatera Fish Poisoning in San Francisco, California, Caused by Imported Barracuda

RICHARD J. GELLER, MD
Fresno, California

KENT R. OLSON, MD
PIERRE E. SENÉCAL, MD
San Francisco, California

CIGUATERA FISH POISONING is endemic to tropical waters, where reef-dwelling fish ingest toxins produced by the dinoflagellate *Gambierdiscus toxicus*. The disease, which is caused by the ingestion of fish contaminated with ciguatera toxins, produces gastrointestinal and neurologic symptoms. These consist of an early gastrointestinal phase (abdominal pain, vomiting, diarrhea) followed by a neurologic or constitutional phase (pruritus, muscle pain, weakness, "burning tongue," blurred vision, dizziness, headache, and hot-cold reversal). We report an outbreak of ciguatera poisoning that occurred in 1989 in San Francisco, California, caused by barracuda (*Sphyraena* species) imported from Florida. This disease is rare in California, having previously been reported in Monterey, California (caused by mullet imported from Florida), and in the San Francisco Bay Area (jack fish from Midway Island).[1]

Reports of Cases

Four members of a Vietnamese-American family became ill after sharing a meal. The family included a 54-year-old man, a 53-year-old woman, their 21-year-old daughter, and 24-year-old son. All patients were in good health before the meal, which consisted of fresh corn on the cob, commercially canned mushrooms, and steamed fish. Only the fish was eaten by all four people. No shellfish had been ingested.

The fish was said to be a "nhong" fish, described as 1.2 m (4 ft) long with a pointed snout. It was purchased from an open-air farmers' market in San Francisco. The family purchased and ate only the head of the fish, which they said was large and contained abundant flesh. Investigation by the county health department determined that the fish eaten was from a shipment of frozen barracuda flown in from Fort Pierce, Florida, and apparently sold to several Asian-American families.

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From the San Francisco Bay Area Regional Poison Control Center, San Francisco General Hospital Medical Center (Drs Olson and Senécal), the Fresno Regional Poison Control Center, Fresno Community Hospital and Medical Center (Dr Geller), and University of California, San Francisco, School of Medicine. Dr Senécal is a Clinical Pharmacology and Toxicology Fellow of the Fonds de la recherche en santé du Québec.

Reprint requests to Richard Geller, MD, Fresno Regional Poison Control Center, Fresno Community Hospital and Medical Center, PO Box 1232, Fresno, CA 93715.

Case 1

At five hours, the father complained of weakness, burning of the tongue, and blurred vision. He became profoundly weak and by eight hours could not get up off the floor. He had no nausea, vomiting, or diarrhea. Paramedics found the patient prostrate with a pulse of 40 beats per minute and a systolic pressure of 80 mm of mercury. He did not have chest pain, and there were no signs of heart failure. Atropine sulfate, 0.5 mg, was administered intravenously (IV). Twenty minutes later, his blood pressure was 132/52 mm of mercury, and his pulse was 88 beats per minute.

In the Emergency Department at San Francisco General Hospital, he had numbness to the face and extremities, weakness, and periumbilical abdominal pain. His blood pressure was 144/90 mm of mercury, pulse rate 84 beats per minute, and he was afebrile. Initial laboratory values included a leukocyte count of 9.0×10^9 per liter (9,000 per μl), hemoglobin 120 grams per liter (12.0 grams per dl), and hematocrit 0.37 (37%). The serum glucose level was 12.7 mmol per liter (229 mg per dl), blood urea nitrogen 7.9 mmol per liter (22 mg per dl), and creatinine 106.1 μmol per liter (1.2 mg per dl). Serum sodium was 139, potassium 3.3, chloride 103, and bicarbonate 27 mmol per liter. Arterial blood gas determinations with the patient receiving supplemental oxygen showed a Po_2 of 344 mm of mercury, a Pco_2 of 44.8 mm of mercury, and pH 7.35.

Because of abdominal pain, a surgical evaluation was done. Bradycardia and hypotension recurred, but additional atropine was not given. Instead, fluid administration was begun. After six hours, he had received 4,000 ml of fluid IV and his systolic blood pressure had still fallen to 70 mm of mercury, with a pulse of 54 beats per minute. An abdominal x-ray series was initially read as showing free air under the diaphragm. A subsequent exploratory laparotomy revealed no intra-abdominal disease.

His hospital course was remarkable for persistent weakness, recurrent bradycardia, and hypotension. His pulse rate stayed between 45 and 55 beats per minute with systolic blood pressures in the range of 80 to 90 mm of mercury. He tolerated these values generally without symptoms and was discharged after nine days.

Two days later, he was readmitted with severe pruritus unresponsive to the administration of diphenhydramine hydrochloride, which had led to a significant cellulitis around his buttocks and presacral area due to excoriation. Mild orthostatic changes in pulse and blood pressure were noted but did not cause symptoms.

Case 2

At 12 hours, the mother became ill in the emergency department while waiting for her husband. She complained of fatigue, nausea, and chest pain. Initially her pulse rate was 68 beats per minute and her blood pressure was 132/90 mm of mercury. At 18 hours, she had nausea and vomiting and complained that her face and throat felt swollen. Her blood pressure was then noted to be 80/38 mm of mercury, and her pulse was 60 beats per minute. Thereafter, her pulse and blood pressure remained low.

Initial laboratory tests revealed a leukocyte count of 11.6×10^9 per liter (11,600 per μl), with 0.69 granulocytes and 0.27 lymphocytes; hemoglobin 122 grams per liter; and hematocrit 0.375. Serum sodium was 141, potassium 3.8,

chloride 104, and bicarbonate 22 mmol per liter. A glucose level was 7.8 mmol per liter (140 mg per dl), blood urea nitrogen 7.1 mmol per liter (20 mg per dl), and creatinine 61.9 μmol per liter (0.7 mg per dl). Arterial blood gases measured with the patient receiving 100% oxygen showed a Po_2 of 499 mm of mercury, a Pco_2 of 53.8 mm of mercury, and a pH of 7.27.

Her gastrointestinal symptoms resolved within 24 hours of admission. She had prolonged and severe bradycardia and orthostatic hypotension, treated with IV fluids with transient benefit. Her resting pulse was about 50 beats per minute, with resting systolic blood pressures averaging 80 to 88 mm of mercury. Standing blood pressures were about 60 mm of mercury, with the pulse increasing to only 80 beats per minute.

On day 9, the patient's supine blood pressure was 106/68 mm of mercury and the pulse was 48 beats per minute. After standing for a minute, her pulse was 83 beats per minute and her blood pressure was 58/39 mm of mercury. After eight minutes of standing, the patient reported dizziness and a sensation of blindness. Her blood pressure was 47/30 mm of mercury, and the pulse was 87 beats per minute. She was returned to the supine position with a prompt resolution of symptoms. Atropine sulfate was then administered intravenously. A total dose of 2 mg given in 0.5-mg increments over 30 minutes completely abolished the orthostatic hypotension. Lasting recovery from symptomatic orthostatic hypotension did not occur until four weeks after the onset of the illness. Severe pruritus developed on the 12th day.

TABLE 1.—*Onset of Symptoms in Patients With Ciguatera Fish Poisoning*

Symptom	*Patients, No. (%)*	*Range of Onset, days**	*Average Day of Onset*	*Median Day of Onset*
Pruritus	16 (100)	1-16	1.8	3
Weakness	15 (94)	0-3	0.7	0
Muscle pain	15 (94)	0-3	0.8	1
Abdominal pain	12 (75)	0-1	0	0
Vomiting	11 (69)	0	0	0
"Burning" tongue	11 (69)	0-3	0.9	0
Blurred vision	9 (56)	0-15	2.2	0
Dizziness	9 (56)	0-7	0.9	0
Diarrhea	9 (56)	0	0	0
Metallic taste	8 (50)	1-7	3.0	3
Headache	8 (50)	0	0	0
Hot-cold reversal	8 (50)	1-7	2.1	1.5
Lip numbness	6 (38)	0-2	0.8	1
Finger or toe numbness	6 (38)	0-4	1.8	1.5
Skin rash	5 (31)	2-14	5.2	7
Dyspareunia (♀)	5 (31)	4-6	4.8	4.5
Joint pain	5 (31)	1-3	1.3	1
Dysuria	5 (31)	0-3	2.0	3
"Burning" feet	5 (31)	0-2	0.5	0
Dry mouth	4 (25)	0-14	5.0	1
Dentalgia	3 (19)	0-14	5.7	3
Nasal burning	3 (19)	0-4	2.0	2
Vertigo	2 (12)	0	0	0
Anorexia	2 (12)	1-8	4.5	4.5
Hiccups	1 (6)	13	13.0	13
Painful intercourse (♂)†‡	1			

*Day 0=day of exposure.
†This symptom occurred in a man who had not eaten the fish but whose wife had, when he later had intercourse with her.
‡Data are not available for the onset of symptoms.

Case 3

At five hours, the daughter had nausea, vomiting, and an unusual "burning" sensation of the tongue, plus mild weakness. She did not seek medical attention. At 22 hours, she presented to the emergency department, where she was evaluated for vomiting, weakness, and burning in the tongue and was released. The daughter returned at 74 hours complaining of a freezing sensation while stepping into a tub of hot water (hot-cold reversal) and generalized weakness. She was again released.

Case 4

At 22 hours, the son also presented to the emergency department, complaining of perioral paresthesias and burning of the tongue. He reported having vomited at 14 hours. He was released. Eight days later, he returned with severe pruritus and excoriation, unresponsive to parenteral diphenhydramine. A regimen of amitriptyline hydrochloride, 25 mg twice a day, hydroxyzine hydrochloride, 25 mg four times a day, and a steroid cream was prescribed. Two days later, he was admitted with a presacral and perigluteal cellulitis due to excoriation. His pruritus had abated slightly.

No family members had rash or immediate pruritus, cranial nerve palsies, or pulmonary symptoms.

Other Cases

On day 8, a family of four ethnic East Indians from the Fiji Islands presented with gastroenteritis to another hospital. Several hours after they had eaten a barracuda purchased on day 1 from the same farmers' market and frozen for a week, they complained of burning of the tongue and perioral paresthesias. One patient had severe bradycardia (pulse rate, 30 beats per minute) and hypotension (systolic blood pressure, 60 mm of mercury); his hospital course was prolonged.

On day 11, two members of a Filipino family who had also eaten barracuda on day 1 presented with severe pruritus. Six other family members who had shared the meal also had symptoms.

All patients identified as having ingested the contaminated fish were contacted and interviewed similarly by staff of the San Francisco Bay Area Regional Poison Control Center. Information collected included the types of symptoms suffered by each patient and the time of the onset of symptoms relative to ingesting the fish. This is presented in Table 1.

Of special interest is a patient who did not eat the barracuda but in whom pain developed at the tip of his penis after intercourse with his wife, who had eaten the fish. Lange and co-workers reported dyspareunia in an unaffected woman following intercourse with her affected male partner.[2] We think that this is the first case suggesting the transmission of symptoms from an affected woman to an unaffected man. A woman who was pregnant at the time of her illness with ciguatera poisoning was delivered of a healthy full-term child five months later.

Discussion

Ciguatera fish poisoning is common in tropical regions between 35° north and 35° south latitude. In the United States, 90% of cases occur in Hawaii and Florida.[3] Sporadic

cases have been reported in Chicago (fish from Florida and the Bahamas),[4,5] Iowa (fish from the Virgin Islands),[6] Texas,[7] Vermont (barracuda from Florida),[8] Maryland (grouper from Florida),[9] and Louisiana, Massachusetts, and Washington, DC.[10] One previous epidemic in the San Francisco Bay Area occurred in 1977 and was caused by jack fish caught off Midway Island and brought by merchant ship into the port of Oakland.[1] A recent report documented an outbreak of ciguatera fish poisoning in ten people who ate fish caught off the middle third of the North Carolina coast on the western edge of the Gulf Stream.[11] The 35°-north latitude line passes through the mid-North Carolina coast.

Fish commonly implicated include barracuda, red snapper, amberjack, and grouper,[3] but more than 400 species have been causative. In a given area, a particular fish is usually responsible. Red snapper is most often the vector in the South Pacific, while in Hawaii amberjack is the most common cause. In Dade County, Florida, where more than a third of barracuda tested have contained ciguatoxin, it is illegal to sell barracuda for human consumption.[12] There are no regulations to prohibit exporting barracuda from Florida or importing it into California.

Pathophysiology

At least three toxins are thought to be responsible for the clinical effects seen in ciguatera fish poisoning: ciguatoxin, maitotoxin, and scaritoxin.[13] The toxins are created by a one-celled organism, the dinoflagellate *Gambierdiscus toxicus.*[14] The organism is similar to the dinoflagellates that cause shellfish poisoning in colder waters,[5] but its growth is restricted to reefs in tropical climates. The dinoflagellate is consumed by small fish, and the toxins are passed on up the food chain as large fish eat smaller fish. The largest fish appear to have the highest concentration of toxin.[15] In some areas, fish are empirically judged as safe or unsafe to eat based on their relative size.

The toxins are lipid-soluble, acid-stable, and are not destroyed by freezing or cooking. They are without taste or smell, making detection difficult.[16] The toxins are concentrated in some organs more than others. Natives of some South Pacific islands test their fish by feeding the liver, ovary, or testis of a fish to cats to observe for signs of illness.

The exact structure, site of action, and mechanism of the toxins are not completely understood. In studies on neuroblastoma cells, ciguatoxin has been shown to act on sodium channels to increase sodium permeability.[17] One site of action appears to be the stimulation of central or ganglionic cholinergic receptors.[13]

Clinical Presentation

Symptoms are largely gastrointestinal, neurologic, and cardiovascular. Neurologic and cardiovascular symptoms, especially pruritus, dizziness, paresthesias, and postural hypotension with inappropriate bradycardia, may be prolonged (months) and severe. Depression has been reported.[5] Symptom patterns vary among ethnic groups and even between the sexes. The sequence of symptom onset may also have a geographic variability. Neurologic symptoms often precede gastrointestinal symptoms in the South Pacific, while the reverse is true in the West Indies.[12] All of our patients had transient, early gastroenteritis followed by prolonged or delayed neurologic symptoms.

The largest series of cases examined in the literature was from the South Pacific.[18] In 3,009 cases, only 3 deaths occurred, each of whom had a neurologic catastrophe (coma, seizures). The distribution by sex was 59.3% in males and 40.7% in females, with 49.7% of cases occurring in the third or fourth decades of life. Common symptoms or signs included circumoral paresthesias (89% of patients), paresthesias of the extremities (89%), burning or pain to skin on contact with cold water (87.6%), arthralgia (85.7%), myalgia (81.5%), diarrhea (70.6%), asthenia (60%), headache (59.2%), and chills (59%). Abdominal pain occurred in 46.5% and hypotension in only 12.2%.

In a series of cases from Hawaii, more than 175 clinical manifestations of ciguatera fish poisoning were reported.[19] Of these, nausea, vomiting, diarrhea, paresthesias (oropharyngeal or acral), and temperature sensation reversal were noted to be common. The last symptom, where hot objects feel cold and cold objects seem hot, occurred in several of our patients on the third day. This phenomenon is strongly suggestive of ciguatera poisoning but is not pathognomonic. It also occurs in neurotoxic shellfish poisoning with exposure to cyclic ethers such as brevitoxins A, B, and C.[20]

Early and persistent hypotension with bradycardia and late, severe pruritus were the most striking features of our cases. Ho and colleagues reported three cases in Toronto, Ontario, that resulted from ingesting grouper from Florida. Profound bradycardia and hypotension occurred in two patients. Late neurologic symptoms—paresthesias, pruritus, and postural dizziness—lasted as long as three months. As in our cases, the outbreak in Toronto occurred in Vietnamese immigrants, suggesting that further outbreaks among Southeast Asians may occur.

Diagnosis is at this time based on the history and clinical presentation. An ingestion of a large fish (especially barracuda or grouper) from tropical reef waters followed by gastroenteritis accompanied by unexpected neurologic and cardiovascular symptoms should suggest the diagnosis. There are no serum or urine tests to detect human poisoning. A radioimmunoassay has been developed that will confirm the presence of ciguatera toxin in suspected fish, but it is not widely available.[21] The remains of one fish eaten by four of our patients were sent to the University of Hawaii for analysis. A stick enzyme immunoassay carried out there was positive in the "high toxic range" for ciguatoxin and related polyethers. Local and state health officials may be able to assist in sending portions of the fish for toxin assay.

Treatment

Treatment is largely supportive. Gastrointestinal symptoms are usually brief and self-limited, requiring little more than the administration of fluids. Mild pruritus will usually respond to antihistamine therapy, but severe pruritus may be difficult to treat. Administering antihistamines and amitriptyline failed to relieve severe pruritus in our patients, but the use of morphine was effective. The relief of neurologic symptoms has been reported with amitriptyline therapy, with variable success.[4-6,22] The use of nifedipine and tocainide has been suggested.[4,23] Intravenous mannitol was given to two patients with suspected cerebral edema and one patient in shock.[24] Recovery within minutes was described. The same study reported further the empiric and uncontrolled use of intravenous mannitol in 21 other patients and claimed a notable lessening of neurologic and muscular symptoms within minutes of administration. In a pilot study from Australia,

infusing 0.5 to 1.0 grams per kg of mannitol (10% or 20%) resulted in "significant" improvement in 5 (42%) and "dramatic" improvement in 3 (25%) of 12 patients with ciguatera fish poisoning.[25] There have been no controlled studies of any of these agents in ciguatera poisoning, and appropriate caution should be used in employing these therapies.

Public health officials should be notified as soon as a case of ciguatera poisoning is suspected, as an epidemic may rapidly unfold. Ciguatera poisoning is not specifically a reportable disease, but it is a food-borne illness. In California, physicians are required to report immediately by telephone when two or more cases or suspected cases of food-borne illness from separate households are suspected to have the same source of illness (title 17, California Code of Regulations, sections 2500, 2504, 2574).

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Sarcoidosis of the Breast, Central Nervous System, and Exocrine Glands in a Patient With Sicca Symptoms

KENNETH H. FYE, MD
RIPLEY H. HUNTER, MD
San Francisco, California

SARCOIDOSIS IS A SYSTEMIC inflammatory disease of unknown etiology characterized by noncaseating epithelioid cell granulomata.[1] The lungs and reticuloendothelial system are typically involved, and virtually any organ system, including the salivary glands, may be affected. Clinical involvement of the breast, however, is exceedingly rare.[2]

Sjögren's syndrome is an autoimmune disorder characterized by keratoconjunctivitis sicca, xerostomia, and clinical or laboratory evidence of systemic autoimmunity.[3] The disorder is pathogenetically defined by mononuclear cell infiltration into exocrine glands, and the diagnosis can be confirmed by minor salivary gland biopsy. Sarcoidosis can also affect exocrine glands and cause sicca symptoms.[4] In such patients, minor salivary gland biopsy will show typical noncaseating granulomata that will distinguish sarcoidosis from Sjögren's syndrome.

Herein we report the case of a woman who presented with sicca symptoms and lymphadenopathy consistent with Sjögren's syndrome and with a hard left breast mass suggestive of breast cancer. Minor salivary gland and breast biopsies revealed only noncaseating granulomata diagnostic of sarcoidosis.

Report of a Case

The patient, a 70-year-old white woman, was seen in November 1989 because of a firm left axillary lymph node enlarged to about 4 cm in diameter. A thorough breast examination revealed no abnormalities. A complete blood count, liver function test values, a chest x-ray film, mammography, and computed tomography (CT) of the chest and mediastinum were all normal. Fine-needle aspirate of the node revealed lymphocytes, histiocytes, and a rare "immunoblastic" cell. The patient refused open biopsy. By April of 1990, she had begun to have neck and jaw pain, xerostomia, and xerophthalmia with significant bilateral submandibular gland enlargement. A needle biopsy of one of the submandibular glands revealed lymphocytic infiltration of benign salivary gland tissue. Treatment with fast-acting nonsteroidal anti-inflammatory agents resulted in symptomatic improvement.

In July, acute diplopia and vertigo developed. On physical examination, the patient had a left lateral rectus muscle palsy, sublingual and labial salivary gland hypertrophy, persistent submandibular gland enlargement, left axillary lymphadenopathy, and a hard mass 3 cm in diameter in the lower inner

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From the Division of Rheumatology, Department of Medicine, University of California, San Francisco, School of Medicine.

Reprint requests to Kenneth H. Fye, MD, 900 S Eliseo Dr, Greenbrae, CA 94904.

quadrant of the left breast. There was no hepatosplenomegaly. A complete blood count and the results of an electrolyte panel, glucose, renal and thyroid function tests, quantitative immunoglobulin assay (IgG, IgM, and IgA), and urinalysis were normal. The erythrocyte sedimentation rate (Westergren) was 19 mm per hour. Liver function test values were normal except for a lactate dehydrogenase of 227 units per liter (normal 90 to 225) and an aspartate aminotransferase (formerly SGOT) of 63 units per liter (normal 0 to 35). The serum calcium level was 2.42 mmol per liter (9.7 mg per dl) and the phosphorus level 1.32 mmol per liter (4.1 mg per dl). The serum angiotensin-converting enzyme level was 1,050 nmol·liter^{-1}·second^{-1} (63 IU/ml; normal < 670 nmol ·liter^{-1}·second^{-1}). A latex fixation test was negative for rheumatoid factor, but the antinuclear antibody assay was positive to a titer of 1:320 (speckled). An x-ray film and CT of the chest were again normal, as was CT of the abdomen. A CT scan of the head with contrast revealed an area of possible enhancement in the suprasellar region. Biopsy of the minor salivary glands showed epithelioid noncaseating granulomata, and stains and cultures were negative for acid-fast bacilli and fungi.

A diagnosis of sarcoidosis was established, but we could not rule out a concurrent and unrelated breast cancer. Therefore, an excisional biopsy of the breast lesion was done. Careful histologic examination revealed only epithelioid noncaseating granulomata and numerous multinucleated giant cells diagnostic of sarcoidosis (Figure 1). There were no signs of malignancy.

A regimen of 40 mg of prednisone per day was started, with plans to taper the dose when clinically warranted. Within a month, the left lateral rectus palsy and vertigo had disappeared and the lymph node and salivary gland enlargement had resolved. Four months later, the patient was asymptomatic on a maintenance dose of 5 mg of prednisone per day.

Discussion

Even though x-ray films and CT scans of the chest were repeatedly normal, our patient clearly had sarcoidosis. First, she had a modest elevation in angiotensin-converting enzyme levels. Although these levels may be elevated in a host of chronic inflammatory disorders, in the proper clinical circumstances, they are strongly suggestive of sarcoidosis.[5]

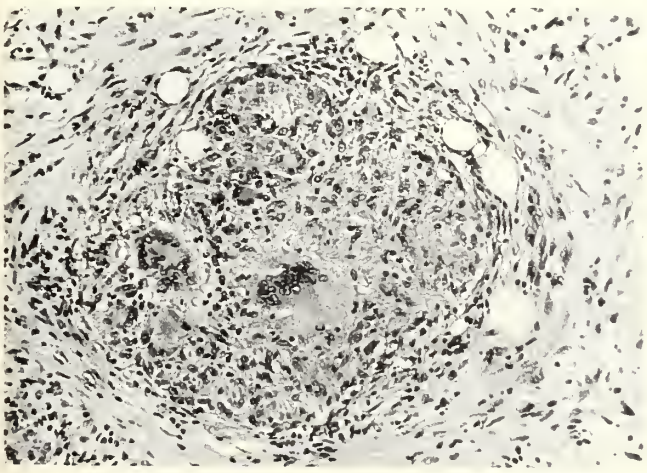

Figure 1.—Histologic examination of a breast biopsy specimen shows a noncaseating granuloma with multinucleated giant cells typical of sarcoidosis (hematoxylin and eosin stain; original magnification × 160).

Second, histologic examination of minor salivary gland and breast biopsy specimens showed multiple epithelioid noncaseating granulomata typical of sarcoidosis. Mycobacterial and fungal infections were excluded by the use of appropriate staining and culture techniques. The presence of antinuclear antibody was not incompatible with a diagnosis of sarcoidosis, as antinuclear antibodies have been observed in sarcoid patients.[6]

The association of sarcoidosis with sicca symptoms is well known. Drosos and co-workers described the cases of five patients with xerophthalmia and xerostomia, documented by a positive rose bengal or Schirmer's test and decreased salivary flow, in whom the diagnosis of sarcoidosis was made by minor salivary gland biopsy (3 patients) or transbronchial lung biopsy (2 patients).[4] The presence of granulomata in minor salivary gland tissue allows clinicians to distinguish sarcoidosis from Sjögren's syndrome because noncaseating granulomata are found in the minor salivary glands of patients with sarcoidosis even when sicca symptoms are not present, but they are not seen in patients with known Sjögren's syndrome.[7] Giotaki and associates found no noncaseating granulomata in the biopsy specimens of minor salivary glands of 28 patients with Sjögren's syndrome, all of whom showed typical lymphocytic infiltration, fibrosis, or both.[8] In patients with sarcoidosis, the finding of noncaseating granulomata in minor salivary glands is often associated with an increased uptake of radioactive gallium into salivary glands, with hilar adenopathy, or with the presence of sicca symptoms.[7] We did not do a gallium scan because the diagnosis of sarcoidosis was made on the basis of a minor salivary gland biopsy done during the evaluation of what we thought was Sjögren's syndrome. Although our patient had dramatic peripheral lymphadenopathy, hilar adenopathy was not observed even with serial x-ray films and CT scans of the chest. Our patient did, however, have sicca symptoms.

Because cranial nerve palsies are characteristic of neurosarcoidosis,[9] we think our patient's lateral rectus muscle palsy was a manifestation of her sarcoidosis. Computed tomography has almost eliminated the need for myelography, air-contrast studies, or angiography in the evaluation of neurosarcoidosis,[10] but magnetic resonance imaging may be even better than CT for assessing intracranial lesions.[11] Because in our patient CT scans were abnormal and a diagnosis of sarcoidosis had already been made on minor salivary gland biopsy, magnetic resonance imaging was not felt to be necessary. The area of contrast enhancement noted in the suprasellar region of our patient is consistent with previous observations that intracranial sarcoid granulomas do enhance with the administration of a contrast medium.[12] The resolution of the lateral rectus muscle palsy was expected because neurosarcoidosis frequently responds to corticosteroid therapy.[11]

Breast involvement is exceedingly unusual in sarcoidosis. In 1978 Rigden reported the development of sarcoidosis of the breast in a 29-year-old woman five years after the onset of pulmonary sarcoidosis.[2] In 1984 Raju and McShine reported the case of a 60-year-old woman who presented with a breast mass suggestive of cancer that proved on excisional biopsy to be sarcoidosis.[13] Two years later Banik and colleagues reported the case of a 28-year-old woman in whom the diagnosis of sarcoidosis was made serendipitously when sarcoid granulomata were found in the mammary lobules adjacent to a fibroadenoma that had been resected.[14] It is known that

sarcoidlike stromal reactions with granuloma formation may be seen in patients with breast cancer,[15] and there may be an increased incidence of breast cancer in patients with a history of sarcoidosis.[16] Therefore, we took special care to be certain there was no evidence of malignancy in the breast biopsy specimen from our patient. The only abnormalities encountered on careful histologic examination of the biopsy specimen were epithelioid noncaseating granulomata diagnostic of sarcoidosis. To our knowledge, this is only the fourth case of sarcoidosis of the breast to have been reported in the English-language literature since 1978.

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Isoniazid Overdose

Successful Treatment With Pyridoxine and Hemodialysis

JOSEPH M. CASH, MD
Rapid City, South Dakota

EDWARD T. ZAWADA, Jr, MD
Sioux Falls, South Dakota

TUBERCULOSIS remains a major public health problem in the developing world. Native Americans, immigrants from the Third World, and immunocompromised patients are the groups in the United States at highest risk. Isoniazid, the hydrazide of isonicotinic acid, is the primary drug prescribed for the treatment of active tuberculosis and the prophylaxis of tuberculosis exposure. Mild, reversible hepatotoxicity is the most common adverse drug reaction associated with therapeutic dosages. Acute neurologic toxicity associated with overdose, however, may be fatal if not recognized and treated promptly. We present a recent case of isoniazid overdose successfully treated with pyridoxine hydrochloride and hemodialysis.

(Cash JM, Zawada ET Jr: Isoniazid overdose—Successful treatment with pyridoxine and hemodialysis. West J Med 1991 Dec; 155:644-646)

From the Department of Internal Medicine, University of South Dakota School of Medicine, Rapid City (Dr Cash), and Sioux Falls (Dr Zawada), South Dakota.

Reprint requests to Edward T. Zawada, Jr, MD, Department of Internal Medicine, University of South Dakota School of Medicine, 2501 W 22nd St, Sioux Falls, SD 57117-5046.

Report of a Case

The patient, a 16-year-old man, was placed on a regimen of isoniazid prophylaxis in November 1988 after the discovery of a 10-mm reaction to a purified-protein-derivative skin test. He had slashed his wrists twice before and had been treated for drug and alcohol abuse. His medical history was otherwise unremarkable. Eight months later, he ingested between 7,500 and 13,500 mg of isoniazid after a disagreement with his girlfriend. He collapsed 30 minutes later and was rushed to a local community hospital, being comatose on arrival. Three seizures were witnessed in the emergency department, whereupon 8.35 grams of pyridoxine and 8 mg of diazepam were infused. The patient regained consciousness and had no further seizures.

He was transferred by air ambulance to Sioux Valley Hospital in Sioux Falls, South Dakota. On arrival, he was alert and fully oriented. Arterial blood gas determinations showed a pH of 7.42, a P_{CO_2} of 29 mm of mercury, and a P_{O_2} of 82 mm of mercury. Other laboratory values included a leukocyte count of 20.1×10^9 per liter (20,100 per μl); hemoglobin 157 grams per liter (15.7 grams per dl); sodium 139, chloride 108, potassium 3.4, and carbon dioxide content 20 mmol per liter; glucose 5.0 mmol per liter (90 mg per dl); creatinine 80 μmol per liter (0.9 mg per dl); blood urea nitrogen 3.2 mmol per liter (9 mg per dl); aspartate aminotransferase (formerly SGOT) 36 units per liter; and alanine aminotransferase (formerly SGPT) 13 units per liter. Isoniazid levels, which were measured by the standard method of Scott and Wright,[1] are shown in Figure 1. Using a femoral vein catheter, hemodialysis was started shortly after admission for several reasons: A Toxline computer search indicated that this patient had ingested nearly double an amount that had previously resulted in death in some patients (80 to 150 mg per kg)[2]; the exact amount ingested was not known, and no charcoal or cathartic mixture had been given to prevent absorption; it was unclear if the initial isoniazid level, which was nearly five times the upper therapeutic level, was a peak or might continue to rise; and he had been symptomatic with the most severe toxic reactions to isoniazid—central nervous system toxicity. No further seizures were noted, and postdialysis isoniazid levels were negligible. He was transferred to a psychiatric facility the following day.

Discussion

Epidemiology

High rates of isoniazid overdose have been reported in Southeast Asian refugee women and Native Americans living on reservations. The government screens all refugees for tuberculosis and treats those with active disease and positive skin tests. The Indian Health Service aggressively identifies contacts of persons with active tuberculosis and provides appropriate treatment.

In Olmsted County, Minnesota, the risk of isoniazid overdose in the Cambodian population is 14 cases per 111 person-years of isoniazid use.[3] Nolan and co-workers estimate that 4.2% of Southeast Asian refugee women between the

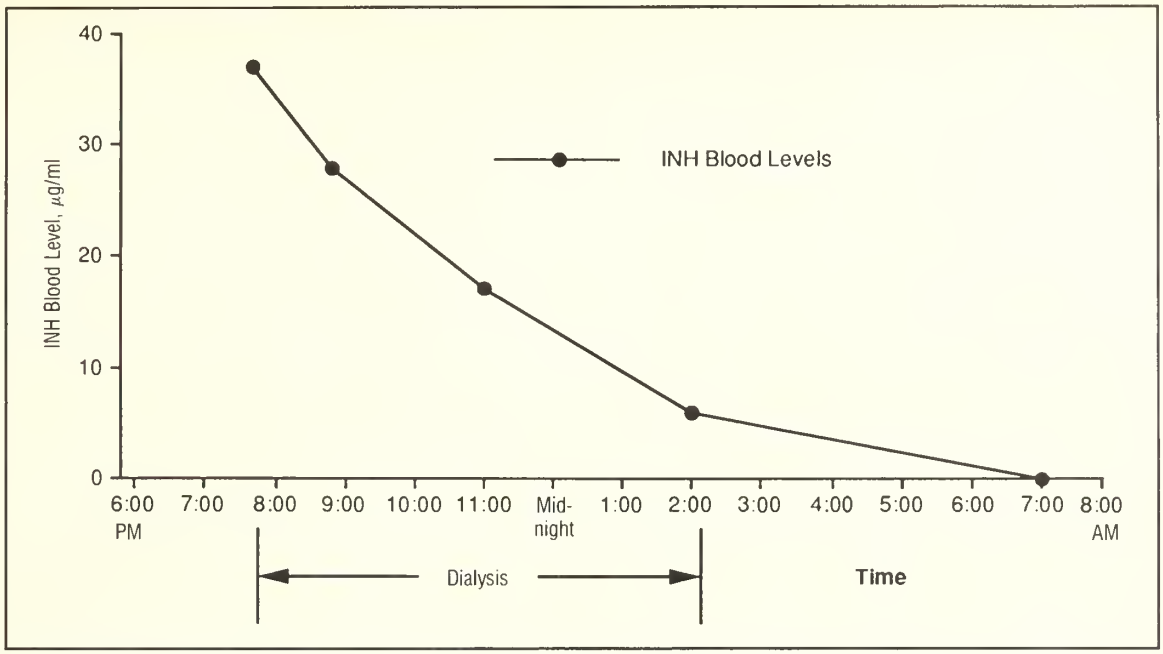

Figure 1.—The graph shows isoniazid (isonicotinic acid hydrazide; INH) levels in blood drawn before, during, and after hemodialysis in a 16-year-old man with seizures.

ages of 25 and 34 overdose on isoniazid while being treated—an extraordinary risk.[4] Depression is the most important risk factor in this group. Many cases, however, are impulsive acts occurring in the context of marital or family problems.

Both suicide and tuberculosis exposure are common in Native Americans.[5] Sievers and colleagues reported that the annual rate of suicide attempts in Arizona Native Americans is 447 per 100,000. Isoniazid was implicated in 8% of suicide attempts and in 17.6% of completed suicides. It was by far the most lethal ingested substance, accounting for 60% of deaths from ingestion. The rate of death from isoniazid overdose was 8.3%, second only to trauma in lethality. Young women were at particular risk for isoniazid overdose. All deaths were associated with ingesting greater than 15 grams of isoniazid and a delay of seeking medical treatment of more than four hours. The rate of isoniazid overdose within a year of starting therapy was 1.2%. The chance of clinical tuberculosis developing was similar to the chance of dying of isoniazid overdose in this group (1/1,400 patient-years versus 1/1,000 patient-years).

Clinical Findings

Ingesting as little as 1.5 grams of isoniazid is toxic in some persons. Consuming 80 mg per kg (sixteen 300-mg tablets in a 60-kg person) or more has a high likelihood of leading to seizures and death if not recognized.[6] Central nervous system effects dominate the clinical symptomatology. The patient may be asymptomatic for as long as two hours. Dizziness, nausea, vomiting, and slurred speech are followed by focal or generalized seizures. Coma may occur at any time. Oliguria and cardiovascular collapse follow in severe cases. Lactic acidosis proportionate to the severity of seizures is common. Severe hepatitis is uncommon. Isoniazid blood levels higher than 10 μg per ml are associated with severe toxicity.[7]

TABLE 1.—*Primary Prevention of Isoniazid Overdose*

Screen patients for suicide risk
Warn parents of the toxicity of isoniazid
See patients frequently to determine compliance
Limit prescriptions to 30 days
Use supervised intermittent therapy in patients at high risk for overdose

Mechanisms of Isoniazid Toxicity

Pyridoxine is an essential cofactor in the production of γ-aminobutyric acid—an important inhibitory neurotransmitter. Isoniazid combines with pyridoxine, forming inactive complexes. This results in a depletion of γ-aminobutyrate levels in the brain, leading to excessive central nervous system stimulation and seizures. The administration of pyridoxine specifically counteracts the neurotoxicity of isoniazid competitively. Studies using dogs[8] show that metabolic acidosis occurs only with major motor seizures and can be prevented by curarization. Correcting the metabolic acidosis does not prevent further seizures. The rate of acetylation (the major route of isoniazid elimination) affects the toxicity of a given dose. Persons in whom acetylation is slow may have greater toxicity at a given dose of the drug.

Primary Prevention of Isoniazid Overdose

Some authors consider isoniazid use to be relatively contraindicated in young female Native Americans[5] and Southeast Asians[4] because of the high risk for suicide and relatively low risk of the activation of tuberculosis. Given the need to eradicate tuberculosis in these groups, however, we propose an alternative approach (Table 1). All patients receiving isoniazid should be screened for depression. Pertinent questions to ask the patient and the family are if the patient's spirits are low or if he or she is losing weight, having difficulty sleeping at night, or has contemplated ending his or her life. Other factors that may increase the suicide risk, such as marital or family problems, school problems, legal problems, the death

of friends or family members, or impulsive behavior, should be excluded. Parents should be warned of the toxicity of isoniazid and should assist in drug administration. All patients should be seen frequently to determine compliance. Weekly visits that include pill counts and blood measurements of isoniazid levels to determine if they are in the therapeutic range are recommended in high-risk patients. Isoniazid prescriptions should be limited to 30 days to reduce the amount of drug available for overdose. Supervised intermittent therapy consisting of 900 mg of isoniazid given twice a week for a year is preferable prophylactic therapy in patients with risk factors for suicide.

Treatment of Isoniazid Overdose

General considerations. Isoniazid overdose can be effectively treated only if suspected. Seizures and coma are due to isoniazid unless proved otherwise in patients with access to the drug. Isoniazid overdose should be a major consideration in patients with status epilepticus poorly responsive to anticonvulsants. Where there is a high concentration of populations at risk for this problem, hospital laboratories should have the capability to measure "stat" isoniazid levels.

Unconscious patients with known or suspected isoniazid overdose should be intubated and lavaged through a large-bore gastric tube to remove any remaining drug from the stomach. Inducing emesis is dangerous in conscious patients because they may seize or become abruptly comatose. The role of activated charcoal slurries and cathartics has not been fully defined.[9] Enough evidence exists, however, to support the administration of 1 gram per kg of activated charcoal immediately after lavage or emesis. Simultaneously, providers should place large-bore intravenous lines immediately and infuse 5% dextrose in a normal saline solution at rates determined by the clinical setting. Vasopressors (dopamine, norepinephrine) are occasionally required. Forced diuresis is not recommended.

Pyridoxine. Pyridoxine is the specific antidote for isoniazid overdose. Physicians should infuse pyridoxine immediately by slow intravenous push (1 gram per minute), even if the patient is fully conscious. The earlier pyridoxine is given, the fewer the complications. The dosage is 1 mg for each milligram of isoniazid ingested. If the amount of isoniazid ingested is unknown or if isoniazid overdose is suspected, infuse 5 grams of pyridoxine. Repeat the initial dose at 5- to 20-minute intervals until the patient becomes stable or the dose of ingested isoniazid is exceeded 1 ½ times by the dose of pyridoxine.[10]

Seizure control. Pyridoxine alone is effective treatment and prophylaxis of seizures in most patients with isoniazid overdose. If seizures are resistant to pyridoxine, infuse diazepam after adequate airway control is established. Phenobarbital also may be used, but phenytoin is not effective. Seizure control is essential to prevent metabolic acidosis. If the pH drops below 7.2, give sodium bicarbonate. Pyridoxine is acidic and should not be mixed with bicarbonate. All patients should be observed for at least four hours after the last seizure.

Dialysis. Hemodialysis rapidly removes isoniazid from the serum.[7] Its use is not necessary in mild cases of isoniazid overdose but should be considered when coma and seizures are not adequately controlled with pyridoxine or when isoniazid levels are extremely high, as in this case. The most severe toxicity occurs with levels greater than 30 μg per ml.[11] An isoniazid level in this range, unless clearly declining on serial measurements when readily and rapidly available, is a reasonable criterion for considering dialysis.[1,11] Peritoneal dialysis also effectively removes isoniazid but is more cumbersome to do than hemodialysis.

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Radiologic Case

A 2-Year-Old Girl With Seizures and Fever

ALICE N. KAROLEWSKI, MD, *and* VIRGINIA C. POIRIER, MD, *Sacramento, California*

A "Radiologic Case" is published in this format on a regular basis. Physicians interested in contributing to the series are encouraged to send their radiologic cases to the series' editor.

JONATHAN M. LEVY, MD
Assistant Editor

A 2-year-old girl was seen because of a three-week history of fever, cough, vomiting, and the recent onset of seizures. She had recently traveled to Mexico. On physical examination, she had a left-sided hemiparesis and a positive Babinski sign on the right. A lumbar puncture was done, and laboratory tests showed a spinal fluid glucose level of 1.7 mmol per liter (30 mg per dl; peripheral glucose 8.2 mmol per liter [147 mg per dl]), protein 1.69 grams per liter (169 mg per dl), and leukocyte count 7,000 × 10^6 per liter (100% lymphocytes).

A contrast-enhanced computed tomographic (CT) brain scan was done (Figures 1-A and -B).

What is the differential diagnosis?

What laboratory or imaging tests would you order to evaluate this patient further?

How would you treat this patient?

SEE FOLLOWING PAGE FOR DIAGNOSIS AND DISCUSSION

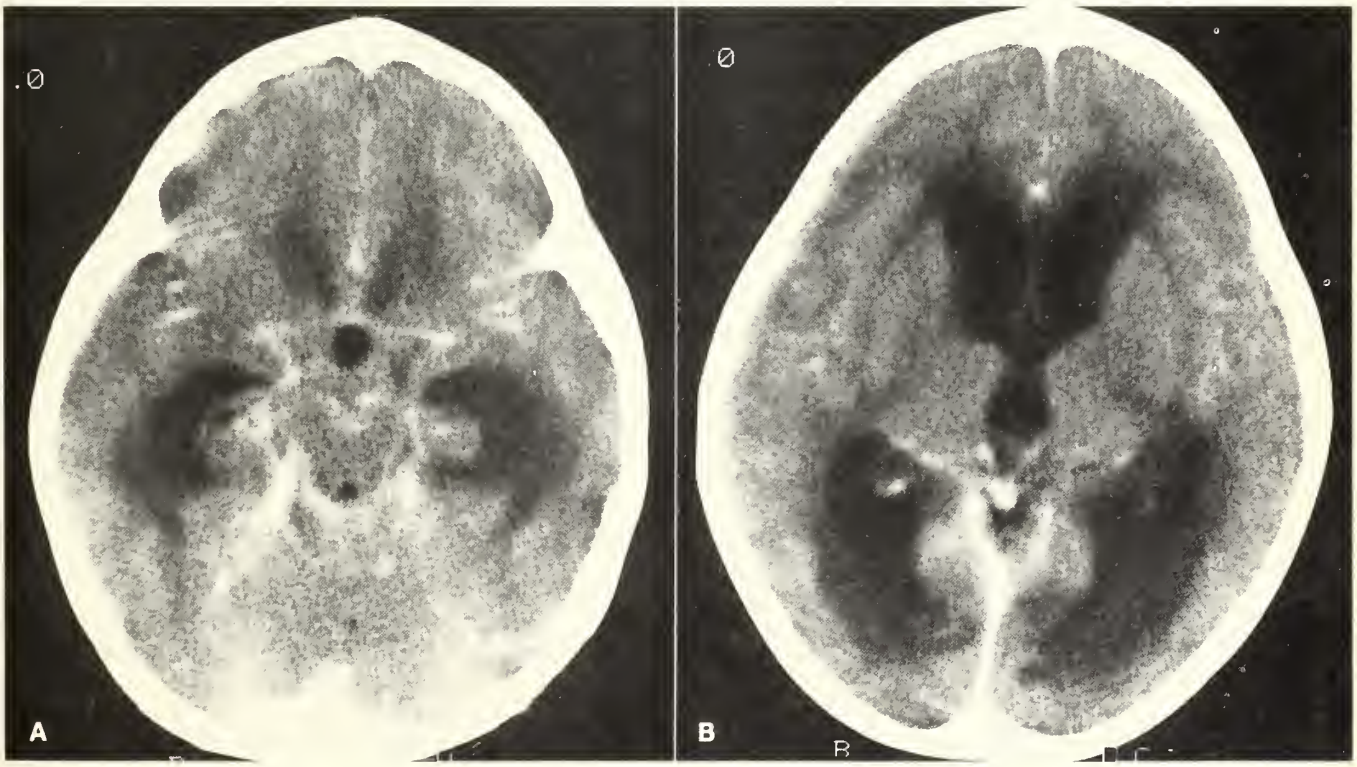

Figure 1.—**A,** The contrast-enhanced computed tomographic (CT) scan shows hydrocephalus with dilated temporal horns. **B,** Hydrostatic edema of the periventricular white matter surrounds the dilated frontal and occipital horns of the lateral ventricles.

(Karolewski AN, Poirier VC: A 2-year-old girl with seizures and fever. West J Med 1991 Dec; 155:647-648)

From the Department of Radiology, University of California, Davis, Medical Center, Sacramento, California.
Reprint requests to Jonathan M. Levy, MD, Department of Diagnostic Radiology, Scottsdale Memorial Hospital, 7400 E Osborn Rd, Scottsdale, AZ 85251.

ANSWER: Tuberculous meningitis

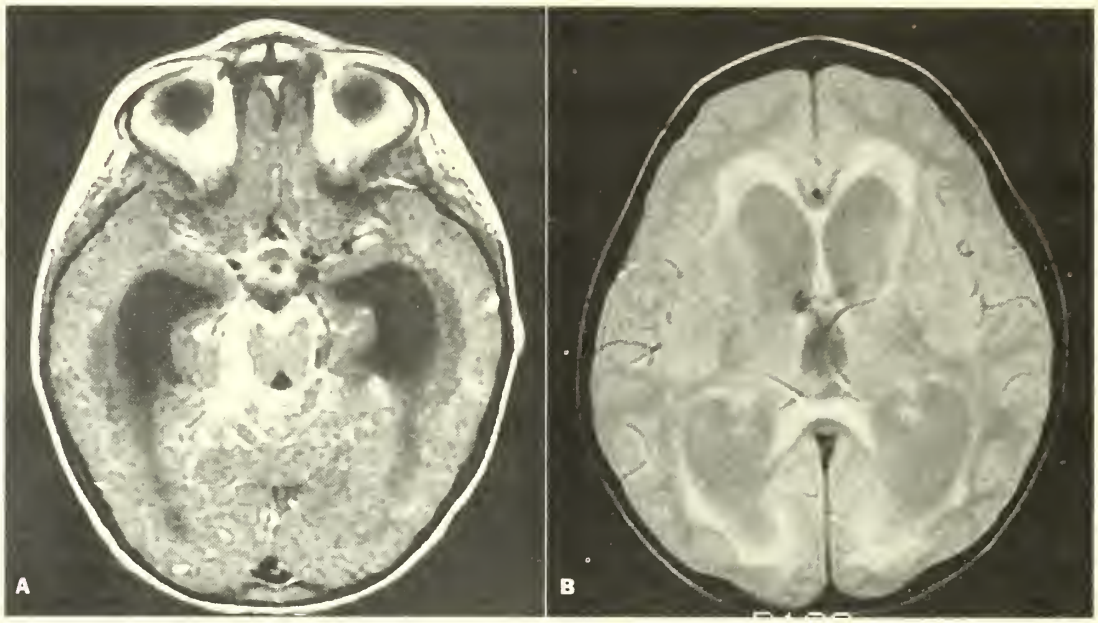

Figure 2.—A, A contrast-enhanced T1-weighted magnetic resonance (MR) examination (TR 500, TE 20) a week after the computed tomographic scan demonstrates abnormal leptomeningeal enhancement around the mid brain, more marked on the right. **B,** A proton density-weighted MR image (TR 2,800, TE 30) shows high-intensity periventricular hydrostatic edema associated with hydrocephalus.

THE CONTRAST-ENHANCED CT scan shows hydrocephalus. Hydrostatic edema surrounds the dilated frontal and occipital horns of the lateral ventricles (Figures 1-A and -B). A contrast-enhanced magnetic resonance (MR) scan was done a week after the CT scan. The T1-weighted image (TR 500, TE 20) shows abnormal leptomeningeal enhancement around the mid brain, more pronounced on the right (Figure 2-A). A proton density-weighted image (TR 2,800, TE 30) shows high-intensity periventricular hydrostatic edema associated with hydrocephalus (Figure 2-B). Based on this appearance, the differential diagnosis would include bacterial and fungal meningitis, leukemia, and meningeal carcinomatosis, as well as tuberculosis. Cultures of spinal fluid were positive for acid-fast bacilli and confirmed the diagnosis of tuberculous meningitis.

Tuberculous meningitis is relatively uncommon in the United States. This diagnosis should be considered if two or more of the following are shown on CT or MR images of the brain: hydrocephalus, leptomeningeal enhancement, basal ganglia and brain-stem infarcts, or tuberculomas.

Hydrocephalus, most commonly communicating in nature, is rarely seen as an isolated finding in tuberculous meningitis. Cerebrospinal fluid obstruction occurs most commonly in the basal cisterns. Computed tomography and MR depict hydrocephalus equally well, but MR is superior in demonstrating the periventricular hydrostatic edema. Abnormal leptomeningeal enhancement may be seen on contrast-enhanced CT scans. Contrast-enhanced MR is more sensitive in detecting active inflammatory and neoplastic processes of the meninges. The enhancement seen in tuberculosis occurs most commonly in the suprasellar and ambient cisterns and the sylvian fissures. The meningeal enhancement seen in tuberculous meningitis may persist as long as a month after therapy is initiated.

Ischemic infarction occurred in 25 of 65 children (38%) with tuberculous meningitis reviewed by Leiguarda and coworkers. Tuberculous infarcts most commonly involve the perforating vessels at the base of the brain. These vessels cross the inflammatory exudate in the subarachnoid space. Infarcts are uncommon in the vertebrobasilar distribution. When basal ganglia infarcts are present, they are frequently associated with brain-stem infarcts, and these are best seen on T2-weighted MR scans.

Tuberculomas, when present, are nodular or ring-shaped enhancing lesions that range in size from 2 to 10 mm. They are located at the base of the brain and in superficial cortical areas and are often multiple. Tuberculomas are best seen on enhanced T1-weighted images and are usually adjacent to areas of marked meningeal enhancement.

The prognosis of tuberculous meningitis remains generally poor, despite effective chemotherapy and normalization of intracranial pressure. Our patient was initially treated with antibiotics but did not respond. A diffuse miliary infiltrate developed in both lungs, typical of tuberculous pneumonia. She was then treated with isoniazid (INH), rifampin, pyrazinamide, streptomycin, and prednisone. The hydrocephalus was treated with a ventriculoperitoneal shunt. Her condition slowly improved, and the patient was discharged five weeks after admission on a regimen of isoniazid and rifampin. She has continued to do well after one year of follow-up.

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Medicine and Society

Participation of Colorado Pediatricians and Family Physicians in the Medicaid Program

STEPHEN BERMAN, MD; STEPHANIE WASSERMAN, MSPH; SUSAN GRIMM, MSPH; *Denver, Colorado*

The Pediatric Health Policy Group of the University of Colorado Health Sciences Center (Denver) surveyed 650 family physicians and 296 pediatricians in 1988, with 50% of family physicians and 48% of pediatricians responding. Half of the pediatricians in private practice and 35% of family physicians in private practice accepted all children who were Medicaid beneficiaries into their practice; 42% of pediatricians and 50% of family physicians accepted all non-Medicaid patients but only some new Medicaid patients; and 8% of pediatricians and 15% of family physicians accepted new non-Medicaid patients but no Medicaid patients. Practice location was associated with the level of Medicaid participation for these primary care physicians: Significantly more rural pediatricians and family physicians than those with urban practices accepted Medicaid patients. The average reimbursement level for these physicians was shown to be an important determinant of whether physicians would accept Medicaid patients. Nonparticipatory physicians were more concerned about excessive paperwork compared with physicians with limited participation. Among physicians with limited participation, family physicians and pediatricians both cited problems of excessive paperwork, reimbursement delays, and retroactive denials of payment as important deterrents to accepting Medicaid patients.

(Berman S, Wasserman S, Grimm S: Participation of Colorado pediatricians and family medicine physicians in the Medicaid program. West J Med 1991 Dec; 155:649-652)

The number of uninsured poor children living in Colorado has increased steadily during the past decade. Studies have documented higher infant and childhood mortality rates for uninsured low-income children[1-3] and a lower number of physician visits when serious health problems exist[4,5] compared with insured children from higher socioeconomic levels. Concerns with the health problems of poor children led Congress for the past three years to pass legislation expanding the Medicaid program to include more poor uninsured children.

The number of Colorado children and adolescents enrolled in Medicaid increased from 73,430 in 1983 to 90,197 in 1989, an increase of 23%. The Omnibus Budget Reconciliation Act (OBRA) 1989 Medicaid expansion that went into effect April 1, 1990, is expected to enroll 16,000 additional children and the 1990 OBRA an additional 1,700 children a year for the next 12 years. To provide care for these newly eligible children, pediatricians and family physicians in private practice will need to be encouraged to care for more children who are Medicaid beneficiaries. Three serial national surveys carried out by the American Academy of Pediatrics in 1978, 1983, and 1989 document declining levels of physician participation in Medicaid, however.[6-8] The proportion of pediatricians willing to care for some patients with Medicaid decreased from 85% in 1983 to 77% in 1989, and the proportion who restricted the extent of their participation grew from 26% to 39%. Unfortunately, Medicaid participation declined as the number of pediatricians in a geographic area increased.

Concern has been raised about the declining participation of primary care physicians in Colorado and its adverse effects on the health of children. We surveyed pediatricians and family physicians to determine the extent of pediatrician and family physician participation in Medicaid, factors that reduce participation, the reasons physicians cite as important in making their decisions to participate in Medicaid, and changes that might encourage more physician participation.

Methods

The Pediatric Health Policy Research Group of the University of Colorado Health Sciences Center conducted a survey of pediatricians and family physicians in collaboration with the Colorado Chapter of the American Academy of Pediatrics and the Colorado Academy of Family Physicians. Surveys were mailed in July 1988 to 650 family medicine physicians and 296 active pediatricians; 270 were in private primary care practice and 26 in subspecialty practice. A follow-up request with an additional survey was mailed in August to nonresponders.

Physicians were categorized as participating or nonparticipating, based on criteria proposed by Yudkowsky and

TABLE 1.—*Participation in Medicaid by Private Practice Physicians in Colorado*

Level of Participation	*Primary Care Pediatricians (n=84), No. (%)*	*Subspecialty Pediatricians (n=22), No. (%)*	*Family Physicians (n=262), No. (%)*	*All Physicians (n=368), No. (%)*
Nonparticipating	7 (8)	1 (4)	40 (15)	48 (13)
Participating	77 (92)	21 (96)	222 (85)	320 (87)
Limited	38 (45)	7 (32)	131 (50)	176 (48)
Unrestricted*	39 (46)	14 (64)	91 (35)	144 (39)

*χ^2 Test for association, $P=.01$ when all pediatricians are compared with family physicians.

From the Department of Pediatrics, University of Colorado School of Medicine, Denver.
This study was supported in part by the Piton Foundation's Poverty Project, Denver.
Reprint requests to Stephen Berman, MD, Box B032, The Children's Hospital, 1056 E 19th Ave, Denver, CO 80218.

TABLE 2.—*Levels of Participation by Urban* and Rural† Practice Settings in Colorado*

Level of Participation	Pediatricians Urban No. (%)	Pediatricians Rural No. (%)	Family Physicians Urban No. (%)	Family Physicians Rural No. (%)
Limited participation	36 (57)	2 (14)	58 (67)	15 (42)
Unrestricted participation	27 (43)	12 (86)‡	29 (33)§	21 (58)§

*Urban settings include the Denver metropolitan area, Boulder, Colorado Springs, Fort Collins, Greeley, and Pueblo.

†Rural settings include Aspen, Buena Vista, Conifer, Durango, Evergreen, Glenwood Springs, Grand Junction, Montrose, and Sterling.

‡χ^2 Test of association, P=.009; odds ratio 8.0; 95% confidence interval 1.5 to 32.9.

§χ^2 Test of association, P=.018; odds ratio 2.8; 95% confidence interval 1.2 to 6.7.

colleagues.[8] Physicians who care for at least some Medicaid patients were considered participating. Participating physicians were further characterized as "unrestricted" or "limited." Unrestricted participation refers to a physician's willingness to accept all Medicaid children as patients when the practice is at less than full capacity. Limited participation refers to physicians with practices under capacity who accept all non-Medicaid patients but only some new Medicaid patients. Nonparticipating refers to providers with practices at less than full capacity who accept all non-Medicaid patients but no Medicaid patients. The participation of physicians whose practices were at full capacity and were closed to new patients could not be evaluated.

Demographic data collected on physicians included age, sex, practice type, location, and number of years in practice. The extent of participation was assessed by asking what percentage of the provider's pediatric patients were Medicaid beneficiaries and the average number of children with Medicaid seen per month. Physicians were asked to rate the relative importance of reimbursement, malpractice, and patient care issues, as well as the relative benefit of possible improvements in the Medicaid program, on a four-point scale: very important or beneficial, moderately important or beneficial, not very important or beneficial, and unimportant or of no benefit. Physicians were then asked to indicate the percentage of their usual fees that they would require of Medicaid if they were to accept more or all new Medicaid children. Comparisons between groups were evaluated with a χ^2 analysis of association for dichotomous data and t tests to compare means.

Results

Of the surveys mailed to 296 pediatricians, 143 were returned, for a 48% response rate. Of those responding, 106 were in private practice, 84 as primary care pediatricians and 22 as subspecialists. Of the surveys mailed to 650 family physicians, 322 were completed and returned, for a 49.5% response rate. Of these physicians, 262 were in private practice. Nonresponders were sent another survey by mail with a letter from their respective professional societies. No attempt was made to conduct a random sample of nonresponders by telephone or further mailings because of financial and resource limitations. It is not possible to know how nonresponders might differ, so our findings should not be generalized to all pediatricians and family physicians in Colorado. Information obtained from approximately half of the primary care physicians in the state, however, is useful in designing strategies to encourage participation in Medicaid for this group of physicians.

The levels of Medicaid participation for 106 pediatricians and 262 family physicians who see children in their private practices are shown in Table 1. Among respondents, more pediatricians than family physicians reported unrestricted participation. The difference in the rates of unrestricted participation between subspecialty and primary care pediatricians was not significant.

The reported mean proportion of physician practices composed of Medicaid beneficiaries and the average number of visits per month varied considerably. Standard deviations were large, and the large variation compromised the usefulness of the analysis.

Factors Influencing Level of Participation

The factors found to be most strongly associated with unrestricted participation were location, type of practice, age, and years in practice. Practice location in an urban or rural site was significantly associated with the level of participation for both primary care pediatricians and family physicians (Table 2). Among respondents, a higher proportion of rural primary care pediatricians and family physicians had unrestricted participation than urban physicians.

The type of practice was analyzed by the level of participation (Table 3). While more solo and partnership pediatricians tended to have unrestricted participation than those working in other types of practice, the differences were not significant.

Family physicians with unrestricted Medicaid participation were older (49.3 years; $P = .0006$) with more years in practice (18.8 years; $P = .001$) than those with limited participation (42.5 years, 13.4 years). There were no significant differences in age or years of practice for primary care or subspecialty pediatricians with limited versus unrestricted participation.

Pediatricians and family physicians were asked to rate the relative importance of reimbursement and patient care issues on their decisions regarding participation in Medicaid. The

TABLE 3.—*Type of Practice by Level of Participation in Medicaid*

Type of Specialty	Sample Size	Type of Practice, No. (%): Solo	Partnership	Group	Other
Primary Care Pediatricians					
Limited participation	38 (49)	10 (42)	9 (39)	15 (60)	4 (80)
Unrestricted participation	39 (51)	14 (58)	14 (61)	10 (40)	1 (20)
Subspecialty Pediatricians					
Limited participation	7 (33)	2 (33)	1 (25)	4 (36)	0
Unrestricted participation	14 (67)	4 (67)	3 (75)	7 (64)	0
Family Physicians					
Limited participation	75 (59)	24 (51)	22 (67)	28 (64)	1 (50)
Unrestricted participation	52 (41)	23 (49)	12 (33)	16 (36)	1 (50)

TABLE 4.—*Issues That Pediatricians and Family Physicians Report as Very Important in Limiting Participation in Medicaid*

Issues	Pediatricians: Limited Participation (n=38) No. (%)	Pediatricians: Non-participation (n=7) No. (%)	Family Physicians: Limited Participation (n=131) No. (%)	Family Physicians: Non-participation (n=40) No. (%)
Reimbursement Issues				
Insufficient reimbursement	25 (66)	5 (71)	95 (73)	27 (68)
Too much paperwork*	14 (37)	5 (71)	71 (54)	28 (70)
Delays in reimbursement	15 (40)	2 (29)	71 (54)	22 (55)
Retroactive payment denial	16 (42)	3 (43)	76 (58)	29 (73)
Difficulty in determining payment due	9 (24)	0 (0)	44 (34)	18 (45)
Patient Care Issues				
Local hospitals will not accept patients	1 (3)	0 (0)	12 (9)	6 (15)
Difficulty with prior authorization	1 (3)	1 (14)	17 (13)	7 (18)
Hampers ability to attract patients	3 (8)	1 (14)	16 (12)	4 (10)
Medicaid patients are unreliable	18 (47)	1 (14)	49 (37)	11 (28)
Improvements to Encourage Participation				
Increased reimbursement	32 (84)	6 (86)	105 (80)	33 (83)
Quicker claims processing	27 (71)	4 (57)	80 (61)	27 (68)
Less complicated paperwork	25 (66)	5 (71)	87 (66)	30 (75)
Prepayment for services	8 (21)	0 (0)	21 (16)	7 (18)
State insurance with limited liability for Medicaid patients	17 (45)	1 (14)	50 (38)	12 (30)

*χ^2 Test of association comparing nonparticipating with limited participation physicians, $P = .023$; odds ratio 0.43; 95% confidence interval, 0.20 to 0.9.

various issues seen as very important to the decision to limit or not participate in Medicaid are shown in Table 4. A higher proportion of nonparticipating physicians than physicians with limited participation cited excessive paperwork as important. Nonparticipating family physicians were more likely than family physicians with limited participation to cite retroactive denials of payment as very important (not significant). Among those with limited participation, a higher proportion of family physicians than pediatricians cited problems of excessive paperwork, reimbursement delays, and denials as most important. The difference between family physicians and pediatricians for each issue was not statistically significant, however. Family physicians were generally more concerned about reimbursement delays than were pediatricians.

Examples of excessive paperwork cited included confusing and cumbersome Early Periodic Screening Diagnostic Testing forms, the need to conform exactly to diagnostic nomenclature when submitting bills, and other confusing billing regulations. Physicians occasionally complained about difficulty in verifying whether a patient was still on Medicaid. Some county social services offices refused to provide physicians with clients' Medicaid numbers. Physicians complained that they experienced delays when attempting to call the fiscal agent for verification. Payment denials did not always clearly state the reason for the denial. Physicians could not determine when a denial was related to a claim for a patient who was no longer a Medicaid beneficiary versus one that was incorrectly filed.

Physicians also were asked about the benefit of possible improvements in the Medicaid system benefit (Table 4). More nonparticipants versus limited-participation pediatricians cited less complicated paperwork as very important. Among family physicians, a similar proportion of nonparticipants and limited participants cited increased reimbursement as most beneficial. Pediatricians with limited participation were as likely as family physicians with limited participation to cite increased reimbursement as very beneficial.

Physicians were asked to identify the percentage of their usual fee that they would require from Medicaid if they were to see all Medicaid children (Table 5). In all, 63% of pediatricians and 72% of family physicians with limited or nonparticipation in Medicaid identified an acceptable reimbursement level. The average level was 84% of usual fees for pediatricians and 85% for family physicians. The data suggest a nonlinear relationship between reimbursement rates and unrestricted participation. An increase in reimbursement from 60% to 80% of the usual fee would increase the proportion of physicians with limited or no participation who would change to unrestricted participation from 8% to 12%. An increase from 80% to 90% would increase the proportion with unrestricted participation by 28%.

Discussion

In Colorado, unrestricted Medicaid participation varied significantly by a physician's location. A 1989 American

TABLE 5.—*Relationship Between Reimbursement Level and Unrestricted Participation by Physicians Who Limit or Do Not Participate in Medicaid*

Reimbursement as a Percentage of Usual Fee	Primary Care Pediatricians (n=53) No. (%, cumulative)	Family Physicians (n=92) No. (%, cumulative)
60%	8 (15)	1 (1)
65%	1 (17)	0 (1)
70%	2 (21)	2 (3)
75%	3 (27)	5 (9)
80%	19 (62)	37 (49)
85%	7 (75)	8 (58)
90%	8 (90)	17 (76)
95%	0 (90)	2 (78)
100%	5 (100)	20 (100)

Academy of Pediatrics survey also found physicians' location to be a strong factor, among many others, influencing the level of participation.[8] The findings suggest that outreach efforts to encourage full Medicaid participation should be targeted to physicians in group practices working in urban areas. Our study cannot explain reasons for differences in participation between family physicians and pediatricians. It is possible that a family physician's decision not to accept pregnant women with Medicaid influences the decision to reject their children as patients. This question was not asked in our survey, however. Nonparticipating physicians seem more concerned than physicians with limited participation about excessive paperwork, prior-authorization hassles, payment delays, and retroactive denials. Increasing the reimbursement without addressing these other issues is unlikely to encourage many nonparticipating physicians to enroll as Medicaid providers. Hadley estimated that a 10% increase in Medicaid reimbursement rates in California would result in a 17% increase in physician participation.[9] Our findings suggest that increases in reimbursement below 80% will not substantially increase the participation of those physicians with limited participation. In Colorado, a high proportion of physicians with limited participation indicated a willingness to see all Medicaid patients who seek care if reimbursement rates were raised to 90% of their usual charges.

In response to the findings of our survey, the Colorado Department of Social Services has established working committees with the Colorado chapters of the American Academy of Pediatrics and the American Academy of Family Physicians to encourage full participation in Medicaid. Physician reimbursement for EPSDT well-child care has been increased substantially. Reimbursement for other services is still below 50% of usual fees, however. The fiscal agent has hired more staff to handle verification calls from physicians. An outreach program to train physicians' office staff about Medicaid billing has been implemented. Finally, the professional societies have joined with the Department of Social Services to meet with physicians throughout the state to educate them about the changes and solicit their support for the program. If children who are Medicaid beneficiaries are to receive appropriate primary care, medical societies and social service departments need to work collaboratively to increase physicians' participation.

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Obstetric Care, Medicaid, and Family Physicians

How Policy Changes Affect Physicians' Attitudes

THOMAS S. NESBITT, MD, MPH; JEFFREY L. TANJI, MD; JOSEPH E. SCHERGER, MD, MPH;
and NORMAN B. KAHN, MD, *Davis, California*

Recent expansion of Medicaid eligibility for pregnant women and increased reimbursement to physicians who provide perinatal services were designed to improve access to care. Family physicians provide a relatively high proportion of care to pregnant women on Medicaid, especially in rural areas. We surveyed all family physicians who provide obstetric services in 26 northern California counties regarding these changes and perceived barriers to providing obstetric care to women on Medicaid. Of surveyed physicians who limited the number of their Medicaid obstetric patients, 58% stated that recent Medicaid policy changes had increased their willingness to accept new Medicaid obstetric patients. Despite these policy changes, administrative issues and poor reimbursement were cited as the two most notable barriers to providing obstetric care to women on Medicaid. Fear of being sued by Medicaid patients is still seen as a barrier by physicians who have recently discontinued practicing obstetrics and by those who continue to care for a large number of Medicaid obstetric patients.

(Nesbitt TS, Tanji JL, Scherger JE, Kahn NB: Obstetric care, Medicaid, and family physicians—How policy changes affect physicians' attitudes. West J Med 1991 Dec; 155:653-657)

Prenatal care is recognized as the most cost-effective intervention in reducing infant mortality.[1] Women in low socioeconomic groups, for whom this intervention appears most important in assuring optimal birth outcomes, often have the greatest difficulty obtaining access to such care.[2-5] This situation is worsening in large part because of the reluctance of many physicians to accept obstetric patients who are uninsured or are insured through Medicaid. Low reimbursement, administrative problems, and malpractice issues are the major reasons reported in the literature for physicians limiting Medicaid obstetric patients in their practices.[6,7] Between 1988 and 1990 in the 26 noncoastal northern California counties, the total number of physicians caring for Medicaid (Medi-Cal) obstetric patients decreased from 207 to 166 (a decline of 20%), despite an increase in the total number of Medicaid obstetric patients.[8]

Recent federal legislation has led to revised eligibility requirements that allow more patients to be covered for prenatal care under the Medicaid program. Many states have increased reimbursement levels to physicians for their care of pregnant Medicaid patients. In California, eligibility requirements have been relaxed to allow pregnant women with family incomes twice the federal poverty level to qualify for Medicaid. The physician reimbursement for global obstetric care under Medicaid in California has risen to more than $1,000, with higher rates being paid under special programs. These changes are intended to improve access to care for low-income patients. For this to occur, however, physicians would need to increase their willingness to care for Medicaid obstetric patients.

These changes are particularly important for family physicians, who care for a high proportion of Medicaid patients in many areas, particularly in rural America.[2,9,10] In the western United States, nearly 40% of family physicians still practice obstetrics, representing two thirds of all rural obstetric providers nationwide. In the 26 noncoastal northern California counties, 30% of obstetric care providers are family physicians, and two thirds of these accept Medicaid obstetric patients compared with only about half of obstetricians in the same area.[8]

Our study analyzed the effects of recent Medicaid changes on family physicians providing obstetric care in a 26-county region of northern California and on their willingness to care for obstetric patients covered under Medicaid. We also analyzed perceived obstacles to providing obstetric care to women covered by Medicaid, comparing the answers of family physicians who are continuing to practice obstetrics with those of physicians who have discontinued practicing obstetrics in the past four years.

Methods

The 26 noncoastal northern California counties in which the study was conducted are predominantly rural and represent about 30% of the land mass of California. More than 57,000 births were reported to residents of the study area in 1988—7,000 (12%) more than in the previous year. There was a 10.8% increase in the number of women covered under Medicaid in 1989 compared with 1986.

A postcard survey was sent to 748 family physicians practicing in these 26 counties whose names were obtained through a listing of members and nonmembers of the California Academy of Family Physicians. Physicians were asked if they currently practiced obstetrics, had discontinued practicing obstetrics in the past four years, or had stopped providing

From the University of California, Davis, School of Medicine.

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Reprint requests to Thomas S. Nesbitt, MD, MPH, Department of Family Practice, University of California, Davis, School of Medicine, 2221 Stockton Blvd, Sacramento, CA 95817.

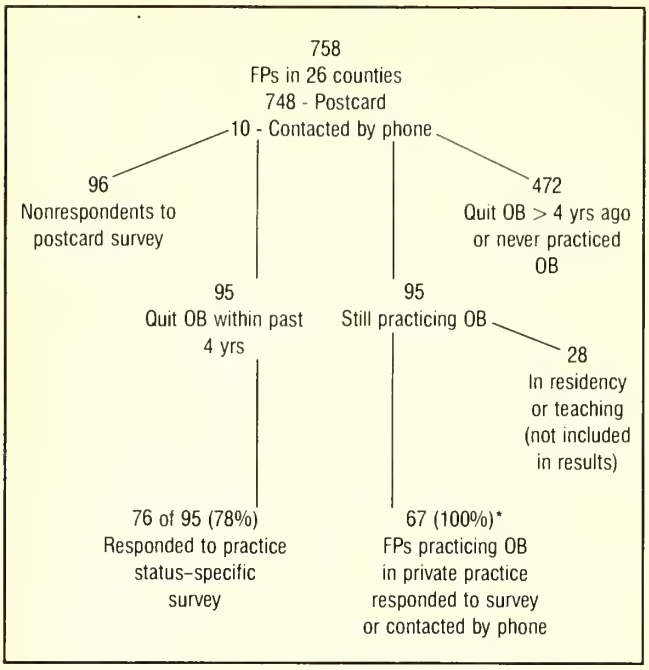

Figure 1.—The response of the study population is broken down according to practice status. FP = family physicians, OB = obstetrics, * = confirmed through contact with area hospitals

obstetric care more than four years before or had never practiced obstetrics. The practice status of 652 of 748 physicians (87%) was obtained through this method. To identify 100% of family physicians performing deliveries, area hospitals were contacted, yielding an additional four physicians who were practicing obstetrics and six who had recently discontinued that practice. These physicians were either not listed with the academy or had not returned postcards. Questionnaires were sent to the physicians who were currently practicing obstetrics or had discontinued practicing obstetrics in the past four years. Two mailings were done. Family physicians who had been identified as practicing obstetrics and who did not respond to either mailing were contacted and surveyed by phone. A breakdown of response rates is given in Figure 1.

Information was obtained on the physicians that included age, years in practice, details on obstetric experience and practice, and the percentage of patients covered under Medicaid. Physicians were excluded if they were in training, if their primary activity was teaching in a residency program, or if they were primarily practicing in military service.

Physicians currently practicing obstetrics were asked if the expansion of Medicaid eligibility or the increase in Medicaid reimbursement had affected their willingness to accept new Medicaid obstetric patients. Physicians still practicing and those who had recently discontinued practicing obstetrics were asked to rank what they considered barriers to caring for Medicaid obstetric patients. Choices on this question included the fear of being sued, administrative problems with Medicaid (delays in reimbursement, paperwork), insufficient reimbursement, Medicaid patients are noncompliant, Medicaid patients are too high risk, concerns about ending up with entire Medicaid families, and practice too full to accept new patients.

Survey responses were evaluated using both a weighted rank order score and a frequency distribution analysis. In profiling physician groups, descriptive statistics were used, including the mean with standard deviation and the median in groups of data with long tails. Student's paired *t* test was used when comparing data between groups.

Results

In all, 44 physicians who had limited their obstetric practice before the changes in guidelines responded to the question regarding the effect of these changes on their willingness to take new Medicaid obstetric patients. Of these, 25 (58%) indicated that the changes in reimbursement increased their willingness to accept new Medicaid obstetric patients.

Physicians who were continuing to practice and those who had recently discontinued practicing obstetrics were asked to rank their perceptions of barriers to providing obstetric care to Medicaid patients (Table 1). Of 67 physicians who continued to practice obstetrics, 57 responded to this question. Among these physicians, insufficient reimbursement and administrative issues with Medicaid (which included paperwork and delays in payment) were ranked as the greatest barriers to caring for these patients in the weighted rank order analysis. These items were also most frequently ranked first or second. The items least frequently ranked first or second among physicians continuing to practice obstetrics were fear of lawsuits and concerns about having to accept an entire family if they accepted a pregnant Medicaid patient.

Of 75 physicians who had recently stopped delivering babies and who responded to our survey, 63 answered the question regarding barriers to caring for Medicaid patients. Among these physicians, insufficient reimbursement and administrative issues with Medicaid also received the highest scores in the weighted rank order analysis (Table 1). Nearly twice as many physicians who had recently discontinued practicing obstetrics ranked insufficient reimbursement as the greatest or second greatest barrier to caring for Medicaid obstetric patients compared with any other barrier. The fear of malpractice suits from the Medicaid obstetric population was a greater concern in this group than among those who are continuing to practice obstetrics.

The mean age of physicians who continued delivering babies was 41 ± 10 years and that of those who had stopped doing so was 44 ± 11 years ($P < .05$). Years in practice for these groups was 10 ± 7 years and 13 ± 10 years ($P < .05$), respectively. The median number of deliveries performed during training for physicians who continued obstetrics (200) was higher than for those who had stopped (150). The median number of deliveries since training was 300 for the continuing group and 200 for the group having recently quit. The median annual number of deliveries performed by physicians who continued practicing obstetrics was 40. The portion of patients covered by Medicaid in the practice was 27% for those continuing obstetrics and 17% for those physicians who had discontinued obstetrics. This difference may be explained in large part by the fact that, in the practices of those who continued practicing obstetrics, 49% of obstetric patients were on Medicaid.

Physicians were grouped by size of obstetric practice and exposure to Medicaid to determine the impact these have on the perceptions of barriers to caring for Medicaid obstetric patients. Family physicians who delivered more than 40 babies in 1989 (high-volume obstetric care providers) considered administrative issues to be the most significant barrier, with insufficient reimbursement and concerns about the high-risk nature of Medicaid obstetric patients following close behind (Figure 2). Among these providers, physicians

TABLE 1.—*Perceived Barriers to Medicaid Obstetric Care*

Practice Status	*Perceived Barriers to Care*	*Frequency Answered 1 or 2*	*Percentage of Total Score*
Continuing Obstetrics (N=57*)	Insufficient reimbursement	20	18.0
	Administrative issues	20	15.8
	Noncompliant patients	19	15.2
	High-risk patients	16	14.7
	Practice too full to accept new patients	18	10.2
	End up with entire family	8	13.3
	Fear of being sued	8	12.8
Discontinued Obstetrics in Past 4 Years (N=63)	Insufficient reimbursement	41	26.7
	Administrative issues	23	20.3
	Fear of being sued	13	14.9
	Noncompliant patients	11	11.1
	High-risk patients	13	10.9
	End up with entire family	8	11.3
	Practice too full to accept new patients	4	4.8

*Four physicians perceived no barriers.

with higher Medicaid obstetric volume (more than 20 Medicaid deliveries in 1989) had the greatest concerns about the high medical risk of Medicaid patients, with administrative and reimbursement issues close behind. Of interest is the fact that the latter subgroup of physicians had more concerns about Medicaid patients suing than did other family physicians currently practicing obstetrics.

Family physicians who delivered fewer than 40 babies (low-volume obstetrics providers) in 1989 ranked insufficient reimbursement as the greatest barrier to caring for Medicaid patients, regardless of the percentage of their obstetric practice covered by Medicaid (Figure 3). Concerns about medical risk and noncompliance were cited as of next importance by this group as a whole (Figure 3). Low-volume providers with more than 50% of their obstetric patients covered by Medicaid considered administrative problems and poor patient compliance to be more important barriers than did physicians with less than 50% of their obstetric patients covered by Medicaid. Fear of being sued did not rank as of high a concern as did other issues among physicians with

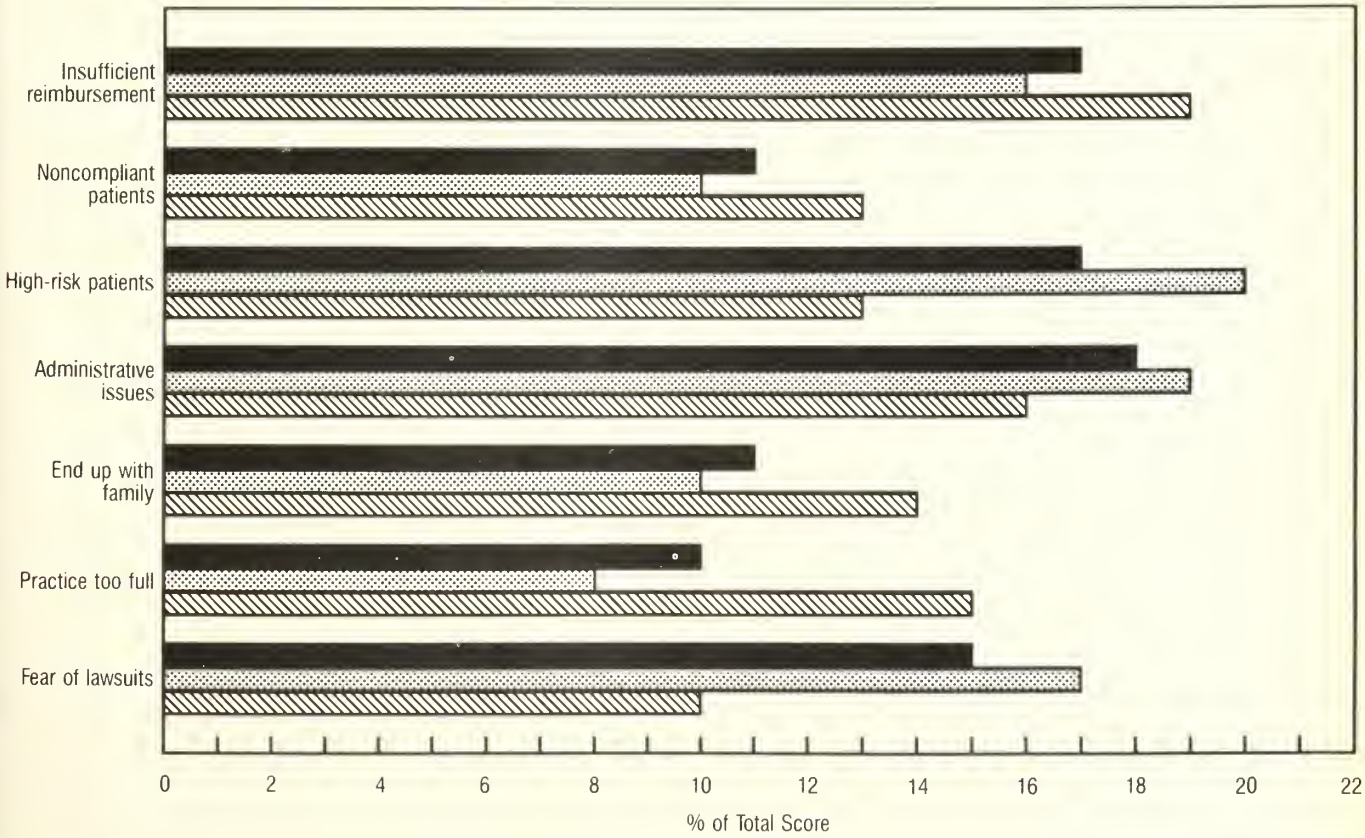

Figure 2.—The graph shows perceived barriers to caring for obstetric patients covered by Medicaid among 31 family physicians delivering more than 40 babies in 1989. ■ = all providers with a high volume of obstetric care, ▨ = providers with a high volume of obstetric care and a high volume of Medicaid patients, ▧ = providers with a high volume of obstetric care and a low volume of Medicaid patients

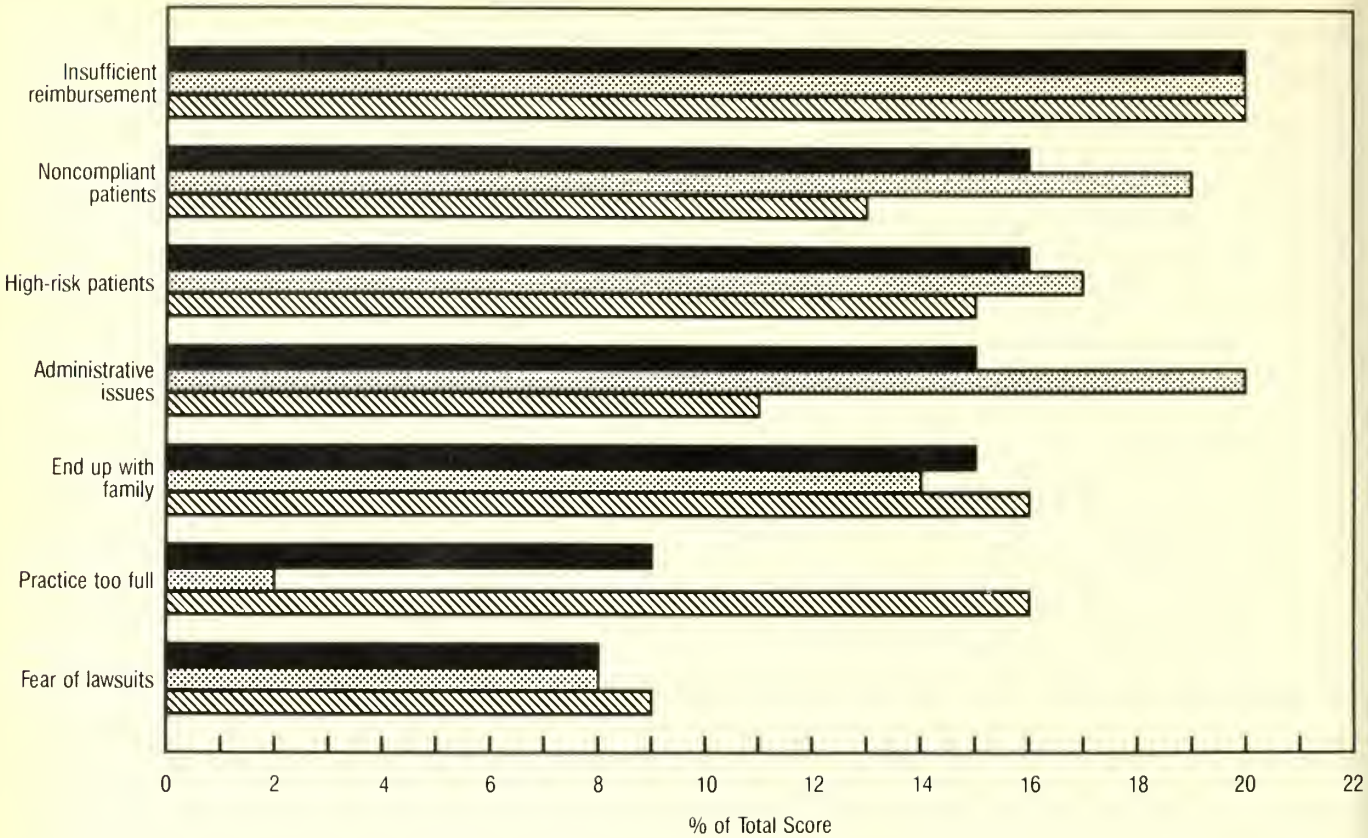

Figure 3.—The graph shows perceived barriers to caring for obstetric patients covered by Medicaid among 26 family physicians delivering fewer than 40 babies in 1989. ■ = all providers with a low volume of obstetric care, ▩ = providers with a low volume of obstetric care and a high volume of Medicaid patients, ▨ = providers with a low volume of obstetric care and a low volume of Medicaid patients

low-volume obstetric practices, regardless of the percentage of Medicaid patients in their practices.

Discussion

The results of this study demonstrate that, for family physicians who practice obstetrics in northern California, increased reimbursement from Medicaid increased their willingness to accept new Medicaid obstetric patients. This study confirms that administrative problems and reimbursement issues are the factors of most concern to both family physicians who currently practice obstetrics and those who recently discontinued this service. These issues have been cited in previous works that included both obstetricians and family physicians.[7] Therefore, not only have the recent changes been on target as far as these physicians are concerned, but also further efforts are probably warranted in these areas.

An issue that does not seem to be consistently a concern among all groups is the fear of lawsuits from Medicaid patients. Family physicians who do more than 40 deliveries a year with a high volume of Medicaid patients and those who have discontinued practicing obstetrics list this as a greater concern than do other groups studied. Interestingly, this has been reported as a persistent concern of obstetricians in one study.[6] A recent study in California, however, has shown that Medicaid obstetric patients do not sue more often than other patients (C. Newhart, S. Teran, B. Aved, et al, "A Comparison of Obstetrical Malpractice Suits Among Medi-Cal Patients Compared to Private Pay Patients in Northern California," unpublished manuscript). That this misperception exists in any group of potential providers of Medicaid obstetric care indicates that state Medicaid programs could benefit by increasing physicians' awareness of Medicaid patients' true propensity for suing.

The critical question remains whether changes in Medicaid eligibility and reimbursement improve pregnancy outcomes. Piper and colleagues showed that, in Tennessee, eligibility expansion alone did not improve early use of prenatal care or outcome.[11] Their study, however, did not adequately address the availability of Medicaid obstetric providers, which in many areas is declining and presumably is the limiting factor in the timing of beginning prenatal care. Our study suggests that increased Medicaid reimbursement will improve access to obstetric care by family physicians.

Some of the physicians we surveyed were not aware of the changes in Medicaid. This situation was also reported in a larger study that included obstetricians conducted in the same geographic area.[8] This suggests that Medicaid programs might be more successful in attracting providers willing to accept their patients if the programs were to increase their marketing efforts regarding policy changes that positively affect physicians.[6] These efforts are already under way in California.

Health care policymakers (state legislators and governors) should continue to strive to bring Medicaid reimbursement closer to that of private insurance companies. It appears that this issue is a major factor in decisions about caring for Medicaid patients. Previous work has demonstrated that dollars spent on providing care for Medicaid patients translate into savings of three to four times by preventing later adverse outcomes.[12] This would argue for states continuing to raise Medicaid reimbursement for obstetric services until an ade-

quate number of providers participate in these programs. In addition, while administrative problems have been addressed in many states, further work clearly is necessary, at least in California. The importance of addressing these issues is increasing as eligibility requirements change and a larger proportion of the population becomes eligible for Medicaid coverage.

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Commentary

Teething as a Cause of Death
A Historical Review

HARRY L. GIBBONS, MD, MPH, *Salt Lake City, and* C. KENT HEBDON, MD, MS, *Sandy, Utah*

Christchurch, New Zealand, May 4, 1876:

> I suppose before now Georgie and Hannah are both walking and hope they are well. You will have to take care of them this next summer and fall *until they get their teeth all cut.* Kiss them all for me until I can return and attend to it myself [emphasis by authors].*

This excerpt is from a letter written to his family by William McLachlan, an early Utah polygamist settler who was then serving as a missionary in New Zealand for the LDS (Mormon) Church. His concern for his two children, ages 14 and 15 months, and their teething status is better understood when we learn that he had already lost a child a few years earlier; the reported cause of death was teething. This unusual diagnosis was listed frequently in early Utah death records.

In the attempt to relate historical diseases with more modern diagnoses, teething as a cause of death has eluded precise linkage. Current medical observations suggest little more than restlessness, drooling, finger sucking, and appetite loss as results of this condition.[1] Previously, however, teething was viewed with great apprehension, as described in a 1975 British article in which Hippocrates is quoted: "Teething children suffer from itching of the gums, fever, convulsions, diarrhoea,"[2(p604)] and Arbuthnot, who wrote in 1732, "Above one-tenth part of all children die in teething (some of them from gangrene)."[2(p1061)] A more contemporary review of questionable diagnoses revealed "teething convulsions" as the reported cause of death in a small group of English children between 1947 and 1979.[3] A 1905 American home health care book contains a description of teething and recommended treatment:

> A very common cause of diseases of the stomach and bowels, and also of convulsions in children, is to be found in the hardening or induration of the gums at the time of teething, and this blunder of nature's ought to be promptly remedied whenever the gums in infants at the time of the first dentition are found to be red, swollen, and hot to the touch, by the use of the lancet.[4(p467)]

*Quotations and information from the letters and journal of William McLachlan were kindly provided by Winifred McLachlan, PHN; the initial data were extracted by David Proctor.

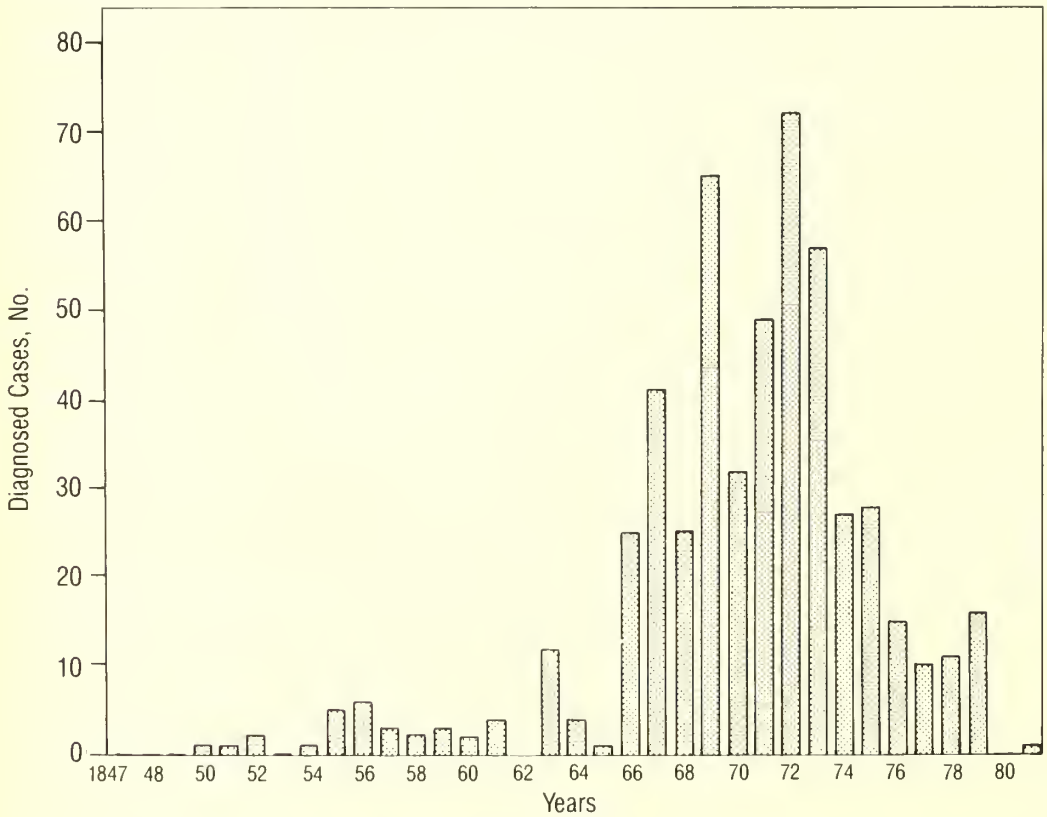

Figure 1.—The graph shows the number of diagnosed cases of "teething" as the cause of death in 19th-century Utah pioneer records.

(Gibbons HL, Hebdon CK: Teething as a cause of death—A historical review. West J Med 1991 Dec; 155:658-659)

From the Salt Lake City-County Health Department and the University of Utah College of Medicine, Salt Lake City.
Reprint requests to Harry L. Gibbons, MD, MPH, Salt Lake City-County Health Department, 610 S 200 E, Salt Lake City, UT 84111.

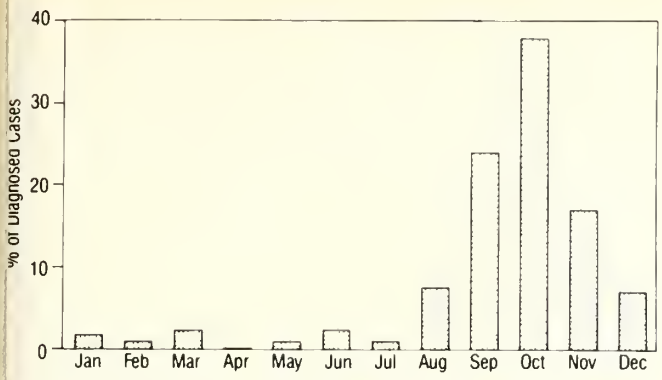

Figure 2.—The graph shows the percentage of teething deaths in the month of occurrence. These figures are taken from Utah pioneer records.

Indeed, significant symptoms associated with teething have a prominent place in the beliefs of many primitive and more advanced cultures.[5] Contemporary American pediatric practitioners are not immune to such beliefs, as noted in a study in which a considerable number of questioned physicians thought teething was related to many systemic symptoms.[6]

Teething Deaths in the Great Salt Lake Valley

Early Utah pioneer records that begin in 1848 list teething as a relatively common cause of death. In the period 1847 to 1881, a total of 521 deaths were attributed to teething or related conditions. Simple analysis of these data reveals two unexpected and unexplained temporal patterns.

The number of cases listing teething as a cause of death increased gradually each year until 1866, when a precipitous jump occurred. The level remained relatively high for several more years. Almost as quickly, the number of "teething deaths" fell (Figure 1) and virtually disappeared. Had a new physician or midwife with a penchant for this diagnosis entered practice, the mystery would be solved. A review of available information on practitioners does not support such a suggestion. Figure 2 shows a second pattern as it plots the number of deaths against the month of occurrence. The vast majority of cases occurred in August through December.

A search of the literature, conversations with historians and pediatricians, and a review of other early records have failed to provide any leads in determining the actual cause(s) of death.

Some have suggested that the actual cause of death was most likely the sudden infant death syndrome (SIDS).[3] In this English study, necropsy reports and death certificates in Sheffield from the period 1947 to 1979 were reviewed. Cases reported to have been due to "convulsions" or "teething convulsions" were dismissed as "cot deaths." Evaluation of Salt Lake City archival data shows the average age for "teething deaths" was 13 months. Most studies have found, however, that SIDS usually occurs before the age of 6 months.[7] This, along with the strong seasonal component noted previously, would not support the teething-SIDS comparison.

Around the time the teething diagnosis was made less frequently, a new cause-of-death entry was increasingly used: "cholera infantium." As with teething, the exact definition of cholera infantium is subject to speculation, although the physiologic mechanism of death is more apparent. The average ages of death were similar, but the peak occurred in August, two months before the October peak of teething deaths. The peak for SIDS deaths in Utah occurs in January but with a number of cases throughout the year, unlike the pattern with teething deaths or cholera infantium.

Conclusion

Teething is a commonly listed cause of death for children in early Utah records. Attempts to equate the diagnosis, with its historical and seasonal variations, to our current understanding of causes of death, including SIDS, have not been successful.

The unraveling of such medical mysteries as this can occasionally provide clues to current problems. More commonly, such endeavors provide an understanding of our medical heritage and fill in a rapidly dimming historical picture that will all too soon be lost to us. We invite comment, conjecture, and facts regarding teething as a possible cause of death.

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Editorials

Why Should Every Physician Know About Hemobilia?

HEMORRHAGE THROUGH THE BILIARY TRACT long remained obscure and was regarded as a medical curiosity but is now steadily rising in importance. Although there were occasional case reports, the first one by Glisson in 1654, the syndrome was practically unknown until about 50 years ago when it received its current name, hemobilia—a linguistic bastard of Greek and Latin. Whereas hematuria, its sister condition, was introduced in the *Index Medicus* from the beginning, more than a century ago, hemobilia does not appear until 1980. With about 25 references annually, it still has only a third of those on hematuria. One reason for the difference might be that tumors in the liver seldom bleed into the ducts, while those in the urinary tract are the main cause of hematuria.

The rise in frequency can be explained partly by a growing knowledge, with fewer cases being overlooked, but it is mainly due to a real increase in occurrence. With more traffic accidents, there are more cases of liver trauma causing central liver ruptures, often a concealed source of hemobilia that is easily missed. Trauma is the most common cause of the pathologic vascular-biliary connection. It is a serious memento to physicians that the incidence of iatrogenic trauma from invasive diagnostic and therapeutic procedures such as percutaneous liver punctures for biopsy, transhepatic cholangiography, and lithotomy is increasing more rapidly than trauma from traffic accidents.

A bleeding source that recently has attracted attention despite its rarity is the pancreatic one, causing what has been called "hemosuccus pancreaticus." In chronic pancreatitis, the lysing effect of extravasating pancreatic juice may cause not only pseudocysts but also pseudoaneurysms of the neighboring splenic artery. When these rupture into the duct of Wirsung, severe colicky pain and gastrointestinal hemorrhage through hemobilia ensue.

There are two main reasons why physicians should be informed of the syndrome. The first concerns major profuse hemobilia. Whereas exsanguinating hemobilia is rare, it must be suspected and promptly recognized because lifesaving procedures might be urgently necessary. An uninformed surgeon may well be mistaken about the bleeding source and perform an inappropriate operation such as "blind gastric resection."

The other reason why knowledge is necessary is that minor hemobilia, with the formation of coagula in the bile ducts, occurs often. The clots are easily mistaken for gallstones and are tempting to be treated aggressively with surgical or endoscoping measures. They will, however, usually resolve spontaneously through the fibrinolytic activity of bile, making operative treatment unnecessary.

If a physician, confronted with the cardinal symptoms of gastrointestinal hemorrhage, biliary colic, and possibly jaundice, suspects hemobilia, he or she has excellent diagnostic means to confirm the diagnosis. Endoscopy will exclude other possible bleeding sources and may demonstrate blood extruding from the papilla of Vater. Selective arteriography is the foremost measure and will generally localize the source of the bleeding, which is essential for treatment. This can be undertaken in direct connection with the diagnostic maneuver by employing the catheter to embolize the responsible bleeding vessel. Embolization is nowadays the primary therapeutic procedure, making operative ligature or liver resection unnecessary.

Most physicians will encounter only a few cases of hemobilia in their career and will thus have to learn about it not through experience but through the literature. The article by Merrell and Schneider elsewhere in this issue presents that information in a most attractive way.[1] With an excellent account of the pathophysiology, they give an accurate description of modern diagnostic and therapeutic methods.

"The light which experience gives us," says Coleridge, "is a lantern on the stern which shines only on the waves behind us." The authors have provided us with an enlightening lantern on the bow.

PHILIP SANDBLOM, MD
Past President, University of Lund, Sweden
Professor Emeritus of Surgery
Centre Hospitalier Universitaire Vaudois
Lausanne, Switzerland

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Dietary Folate—The Digestible Vitamin

FOLIC ACID, a vitamin essential as a cofactor in the synthesis of cellular DNA, is particularly important for the support of tissues such as the bone marrow, intestine, and colon, where cell turnover is brisk. Although the ingestion of supplemental folic acid in its monoglutamate form (pteroylglutamic acid [PteGlu]) is common in young children and during pregnancy, most of us obtain adequate amounts of this vitamin in food as the complexed polyglutamate form (pteroylpolyglutamate [$PteGlu_n$, where the *n* subscript, denoting the number of peptide-linked glutamic acid units, is 2 to 7]).[1] These glutamate residues of the pteroylpeptide are removed sequentially by cleavage from the end of the peptide chain, a reaction catalyzed by folate hydrolase (formerly called folate conjugase), an integral enzyme of the enterocyte brush-border membrane that is available to polyglutamates at the intestinal lumen-cell interface. This is an example of surface digestion by enterocytes that we now know to be an essential digestive step before transport of the final monoglutamate product. Although there are no other known instances of brush-border digestion of a vitamin, intestinal surface digestion of macronutrients at the brush-border membrane surface before entry into the enterocyte was identified many years ago. The brush-border oligosaccharidases[2] (commonly called disaccharidases) cleave lactase, sucrase, and the oligosaccharide products from starch breakdown to monosaccharides; peptidases such as the amino-oligopeptidase[3] (aminopeptidase *N*) and dipeptidylpeptidase[4] remove amino acids from nutrient oligopeptides in preparation for the intestinal transport of dipeptides and amino acids. In these instances of nutrient surface hydrolysis by enterocytes, the oligomeric substrate, not being suitable for transport, must first be cleaved to transportable products.

When both digestion and transport are required by the enterocyte, questions arise concerning their relative rates and

possible interactions. If one process were much slower than the other, then it could be rate-limiting for overall assimilation. Perhaps the smaller intermediate hexaglutamate to diglutamate products of $PteGlu_7$ compete for the PteGlu transporter, thereby slowing its transport rate; or PteGlu, the final product released from hydrolysis, might retain specificity for the hydrolase, bind to its active site, and retard hydrolysis, a process known as product inhibition. To some extent, these cross-inhibitions probably do occur in vivo, but a major inhibitory interaction between the two complementary events of hydrolysis and transport is unlikely to be of physiologic importance. In the rat, a mammal in which there is only a trace of brush-border folate hydrolase, the monoglutamate transport step appears paradoxically to be rate-limiting for folate absorption.[5] But all studies of human folate assimilation indicate that uptake is significantly (about 50%) more rapid from PteGlu than from $PteGlu_7$.[6,7] This has led to the suggestion that hydrolysis is probably rate-limiting. But the definitive answer is not yet in. Whereas the affinity for PteGlu transport appears to be relatively low ($K_m \sim 10$ μmol per liter) at neutral pH, the K_m at the relatively acidic pH (~ 5.5) of the microenvironment of the brush border-lumen interface is about 1 μmol per liter,[8] comparable to that for the polyglutamate hydrolase. Unfortunately, no comprehensive study in humans has compared the maximal rates (V_{max}'s) of the two processes that together define the overall assimilation of dietary folate.

In contrast to the apparently slow rate of polyglutamate hydrolysis, most saccharide and peptide nutrients are rapidly digested at the intestinal surface and provide more than ample monomer (glucose or amino acid) for transport. The sole exception to this is lactose assimilation in which the hydrolysis step is rate-limiting, even for persons who have a full complement of intestinal brush-border lactase.[9] Thus, there is a similarity in the kinetics of polyglutamate and lactose assimilation in humans, both having relatively slow surface hydrolytic processes that may be rate-limiting for assimilation.

Because the hydrolysis of polyglutamate is a relatively slow process required before intestinal transport of the biologically active monoglutamate, an important question comes to mind. Does the cleavage step become impaired even more than the PteGlu transport process in intestinal diseases? In this issue, Halsted reviews the work of his group and others on the intestinal assimilation of polyglutamate and monoglutamate folates.[1] A perusal of Figure 2 of that article allows an approximation of the ratio of $PteGlu_7$ hydrolysis to PteGlu assimilation of about 0.63 to 0.83—that is, the overall assimilation of $PteGlu_7$ (which includes both its hydrolysis and final monoglutamate transport) was 63% to 83% of the absorption of monoglutamate itself. Although there was a dramatic decrease in folate assimilation in intestinal diseases such as celiac sprue and tropical sprue to only 15% to 30% of normal, the impairment of the activity of folate hydrolase, as measured from the in vivo hydrolysis of $PteGlu_7$, was similar to the loss of monoglutamate transporters, as estimated from the $PteGlu_7$/PteGlu ratios (0.50 to 0.83). Only in the case of untreated celiac sprue was there a suggestion of a greater loss of polyglutamate assimilation (about 0.50), perhaps reflecting a selective impairment of polyglutamate hydrolysis out of proportion to that for monoglutamate transport. A similar analysis of the impairment of oligosaccharide assimilation in tropical sprue also has shown a parallel reduction in both hydrolysis and transport, with the exception of a greater impairment of lactose hydrolysis.[9] In essence, then, despite the superficial and seemingly vulnerable location of hydrolases at the enterocyte brush border in intestinal diseases, most integral hydrolytic enzymes do not appear to be hampered more than the membrane transporters that receive the end products.

Nutrients ingested along with dietary polyglutamate may have an effect on its obligatory intestinal surface digestion and subsequent assimilation. Legumes, tomatoes, and orange juice appear to inhibit human brush-border folate hydrolase, while cereal grain flours, milk, cabbage, cauliflower, and lettuce are not inhibitory.[10] In miniature pigs, animals with high amounts of folate hydrolase similar to those in humans, chronic ethanol ingestion inhibits folate hydrolase by about 50% but does not depress the monoglutamate transport process.[11] Although zinc deficiency does not appear to decrease either polyglutamate hydrolysis or monoglutamate transport,[12] zinc does increase folate hydrolase activity while paradoxically interfering with the final PteGlu transport.[13]

Because of the requirement for the surface digestion of dietary polyglutamates before absorption of the monoglutamate end product, interest has arisen in the structure and function of the brush-border polyglutamate hydrolase. Like other brush-border hydrolases, it is a large macromolecule (about 240 kd in pigs and more then 500 kd in humans).[14] Halsted's group[15] noted a predominant subunit of 120 kd in pigs, suggesting it exists in the membrane as a homodimer. An additional 195-kd unit, identified by the immunoblotting of acrylamide gels with specific antibody but not found in immunoprecipitates, may constitute a related macromolecule present in small amounts. Further work will be required to define the exact relationship of this larger species to the 120-kd subunit.

The detailed information now available on the assimilation of dietary folate is matched only by that known for so many years for another important vitamin, cyanocobalamin (vitamin B_{12}) and, more recently, for vitamin D. Regrettably, our knowledge about the many other micronutrients essential for normal tissue function lags far behind that of the macronutrients. It is hoped that an increase in our understanding of molecular events of the assimilation of other vitamins and trace elements will be forthcoming.

GARY M. GRAY, MD
Professor of Medicine
Director, Digestive Disease Center
Stanford University School of Medicine
Stanford, California

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INSERTING A CHEST TUBE WITHOUT ANESTHESIA

All the doctor knows is restricted
to the furnace of my chest.
The infection electrifies my ribs.
When the doctor touches me
he is shocked.
It is small warning.
He leaves me burning
and returns
with the metal dilator.

I tilt on my side, tense
as timber about to fall.
A sterile drape covers
my face and shoulders;
its sheen traps my heat
then transfers it to me.
The doctor wedges the dilator
between my ribs and pounds,
ax to wood, splintering tissue—
how many blows?
I lose count—after one
there are no numbers.

MICHELE WYREBEK©
Sterling, Massachusetts

Correspondence

The Editors will be pleased to receive and consider for publication correspondence containing information of interest to physicians or commenting on issues of the day. Letters ordinarily should not exceed 600 words and must be typewritten, double-spaced, and submitted in duplicate (the original typescript and one copy). Authors will be given the opportunity to review the editing of their correspondence before publication.

Taxes and Abortion

To the Editor: In response to Dr Notkin's letter in your August issue,[1] I believe it is extremely encouraging that the Supreme Court has upheld the government regulation that physicians at family planning clinics should no longer receive federal funds if they choose to discuss abortion with their clients.

This is not primarily an abortion issue but is a monetary issue. If I and many Americans like me choose to believe that abortion is not a viable alternative for unexpected pregnancies, then one of the ways that we support our beliefs is by insisting that we should not have to pay for such counseling through our tax dollars. This in no way eliminates the ability of female clients to hear about the alternative of abortion. These clients are free to go to such centers where it is discussed. The only thing that has changed is that my tax dollars are no longer supporting people who wish to discuss this as an alternative.

This is not a freedom of speech issue. This does not involve infringement upon the traditional right of a physician to discuss freely all medical options with the patient. This is simply a monetary matter, involving the use of my tax dollars and your tax dollars in the ways that we feel they should be spent. No one feels that it would be wrong for anti-war protestors to speak their mind about the use of our tax dollars in supporting wars that they feel are unjust. In like manner, it is not wrong for me to say I do not wish my tax dollars spent in this manner.

LAURA HAMMONS, MD
PO Box 1100
2111 College Dr
Gallup, NM 87301

REFERENCE

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Positive Preemployment Urine Drug Screen Caused by Foreign-Manufactured Vitamin Formulation

To the Editor: We report a case of positive result on a preemployment urine drug screen caused by the ingestion of a vitamin formulation manufactured in El Salvador. The patient, a 35-year-old male applicant, was nearly denied employment because of a positive urine drug screen for benzodiazepines, confirmed by gas chromatography using mass spectrometry (GC/MS). On a preemployment drug history form, the applicant said he had not taken any medications for the past 30 days. After being informed of the test results, he initially denied any illicit or prescription medication use. On detailed questioning, he later acknowledged taking over-the-counter vitamins purchased in Tijuana, Mexico. To evaluate the possibility that the vitamins contained benzodiazepines, he was requested to render the vitamins for forensic analysis. He submitted three individually sealed tablets identified as *"Nervo Tiamin Tranquilizante Vitaminado."* The only listed ingredients were thiamine hydrochloride and meprobamate. Analysis of the tablets by another laboratory using GC/MS revealed the presence of diazepam.

Preemployment drug screen tests are commonly administered for employee selection. This case illustrates the need for a medical review of all positive test results to ensure that applicants are not discriminated against by being falsely classified as illegitimate drug users. A medical review of urine drug screen results is not required for private sector employees not covered by federal regulations, and persons testing positive may be summarily denied employment without any medical review of their test results.

The problem of false-positive test results due to drug cross-reactions with initial screening immunoassays for drugs of abuse has been largely addressed by confirmatory testing using a second specific analytic method such as GC/MS. False-positive test results have been produced by pharmaceuticals including phenylpropanolamine, hydrocodone, ephedrine, and pseudoephedrine. Confirmatory testing, however, does not address the problem of true-positive test results unrelated to illegitimate drug use. True-positive results on urine drug screens have been caused by the ingestion of poppy seed-containing foods that contain morphine,[1] topical anesthetics containing cocaine for dental procedures,[2] and the ingestion of a Chinese medication purchased from a California health product catalog.[3] Herbal coca leaf teas containing cocaine were previously sold in health food stores.[4]

The ingestion of foreign-purchased pharmaceuticals has not been reported as a cause of positive urine drug screen tests. Mexican pharmaceuticals have been reported to contain unidentified steroids and benzodiazepines.[5] Physicians reviewing drug screen results need to recognize that persons residing in close proximity to Mexican communities may purchase foreign-manufactured medications or vitamin formulations that contain controlled substances. Preemployment drug histories cannot be solely relied on for an accurate drug history, and examinees should be interviewed to determine if there is a legitimate medical explanation for a positive test result. Persons ingesting foreign-purchased vitamins or over-the-counter medications may unwittingly ingest drugs that can produce serious side effects and lead to adverse drug interactions.

M. JOSEPH FEDORUK, MD
1401 N Tustin Ave, Suite 240
Santa Ana, CA 92701

LORETTA LEE, MD, MPH
County of Orange, Health Care Agency
801-C N Broadway
Santa Ana, CA 92701

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Lessons From the Practice

The Ill-fated Child

GEORGE ZUCCONI, MD, *La Mesa, California*

Never been lonely
Never been lied to
Never had to scuffle in fear
Nothing denied to

PAUL SIMON, 1991

I am listening to Paul Simon's just-released album, "The Rhythm of the Saints." Primed by the joyous sound of his earlier work in "Graceland," I am eager to hear these new efforts, especially so because I need relief from a sorrowful event that is unfolding. The poignant words cling to the ebullient music in empathy with my own frame of mind.

I envy the person described by the words of the refrain because I long to be free from the burden pressing on me. The cause of my anguish is the discovery of an ill-fated infant. Midway through a pregnancy, after passing through the waves of nausea and skirting the rocks of miscarriage, a woman usually finds herself in calm waters. The swelling weight of the pregnancy has not yet begun to press relentlessly, and labor is not close enough to dampen anticipation with fear. During this lull, the realization of a mother's worst nightmare can be shattering.

In a darkened room, the image on a small video monitor jumps to life as my hand moves the sonogram's transducer over a pregnant abdomen. As the probe moves to and fro, forms begin to take shape on the screen. Every movement of the hand produces a change, like a lump of wet clay taking shape on the potter's wheel. At first the image is a scramble of black and white lines. Then form emerges. The transducer moves. It picks up an arm. The arm is moving. A hand becomes visible. It glides toward the infant's face until the thumb approaches the mouth. It is a motion that convinces any observer of the indisputable humanity of this being under scrutiny.

I stop shifting the probe when I pick up another movement, the rhythmic pulsation of a heartbeat. But there is a distended sac surrounding this tiny heart, and the mounting pressure of the fluid collecting within its confines threatens to squeeze the life out of this feeble pulse. More accumulations of fluid become visible within the membranes surrounding the lungs. It is evident that the baby has severe hydrops, to an extent that survival for much longer is unlikely.

None of this is apparent to the mother watching her infant suck its thumb while the muscle of its heart beats so vividly on the screen. I keep my eyes fixed on the monitor lest they betray this knowledge to her, at least for now. Telling a woman her baby is doomed is a grim duty, and I desperately search for some way to soften the blow.

I am afforded a narrow peak through a small keyhole into the future, and the view is gloomy. I flinch at the disillusion that's coming and wish to be spared this prophecy. I suppose foreknowledge is forewarning, but nothing could ease this woman's reconciliation with her baby's prognosis. At the moment of confrontation, her life would be affected irrevocably. My part in this also affects me, not to any degree comparable to her affliction, but in a more insidious way. It is not my first, nor will it be my last, such encounter, and it is not given to us to know how many of these can be suffered.

After the wave of shock passes, expressions of frustration give way to weeping, and then a look of numbness comes to her face. All emotion is drained. Everything is swept bare. The only thing left to her is to seek assurance that there is some reason for such a mishap, that such a wrong must have something ultimately worthwhile about it. I suppose we need to feel that there is a logic to the universe and cannot easily accept the notion that suffering has no counterpart to even the balance. But I can offer her no such assurance.

Because the baby has scant chance of surviving much longer, my advice is to deliver it now. Although the baby might be born alive, the immaturity of the lungs and the pleuritic effusion would prevent it from breathing. To discuss the living as if they were dead is eerie. To carry out plans that will result in the death of the living is aberrantly bizarre. But this is all I can offer to tip the scales. It would spare this woman the anguish of prolonging the inevitable and harboring the thought that the commemoration of her infant's birth would be a burial.

Labor is made more tolerable by the vision of the pink, cherubic offspring that will soon lie cuddled in loving arms. Who knows what phantasms of misshapen anatomy creep into the mind of a woman in this kind of labor? The tortured mind can conceive of monstrosities more fiendish than exist. The wordless plea for relief from this terror is pitiful. And no matter what I do or say, these apparitions will return to haunt her dreams for a long time to come.

Her labor ends at night. The night brings peace. The tempo is slow. People are quiet. She does not want to look at the dead infant, but it is not abhorrent. The skin of the face is distended by edema. The swelling makes the features look so small that it is the face of a doll, all cheeks and a tiny pursed mouth. It appears to be at peace. No need to hide it in the dark. She sighs the relief of the helpless. The tranquility of the survivor comes over her face as she expresses the gratefulness of the believer. I leave the hospital at midnight, time enough left for renewal before the new day to come.

I look for solace in the mood of "The Obvious Child." A single snare drum rattles barrump-dum-dum, barrump-dum-dum, barrump-dum-dum in the cadence of a march. It is as steady as the drip, drip, drip of the intravenous fluid measuring out oxytocin in labor. The cadence breaks into a synco-

(Zucconi G: The ill-fated child. West J Med 1991 Dec; 155:664-665)

Dr Zucconi is in private practice in obstetrics and gynecology, La Mesa, California.
Reprint requests to George R. Zucconi, MD, 8851 Center Dr, Suite 301, La Mesa, CA 91942.

pated beat, and then several big drums join in with a staccato in a register so low they set something vibrating deep inside. A high-pitched cry of joyous abandon sings out faintly in the distance, aroused by the tumult of the drums. A chorus of basso voices responds with a sound that has escaped from a great depth, as if set free by the booming drums.

Snare drum, bass drums call and answer in a pattern of rhythms—doleful, blissful, visceral—that inflame, that soothe. The percussive detonation of a booming drum, punctuating each phrase and fading with a barely audible vibration, tolls the extremes of life. Its resonance echoes the explosive bellow of birth and the last sigh of death. At the end, a plaintive voice joins in a high-pitched wail, and the resolution of the mystery of life is poised at this equilibrium in the sway between good and evil.

* * *

"Lessons From the Practice" presents a personal experience of practicing physicians, residents, and medical students that made a lasting impression on the author. These pieces will speak to the art of medicine and to the primary goals of medical practice—to heal and to care for others. Physicians interested in contributing to the series are encouraged to submit their "lessons" to the series' editors.

JONATHAN E. RODNICK, MD
STEPHEN J. McPHEE, MD
Series' Editors

Lessons From the Practice

My Own Awakening

ROBERT J. REINER, MD, *Lompoc, California*

Viewing the recently Oscar-nominated *Awakenings* stirred emotions and memories I had not felt since 1959. You see, I essentially lived at the same institution that Oliver Sacks wrote about and that was portrayed in this movie.

Awakenings takes place at The Beth Abraham Home for the Chronically Ill, which is now the Bronx Psychiatric Institution, a part of Albert Einstein Medical Center. The movie takes place in 1969, when Dr Sacks used L-dopa to treat, and place into temporary remission, many postencephalitic patients with parkinsonism.

From 1955 to 1959, my mother, a Hungarian immigrant, was the Director of Nurses at this institution. Every other weekend, on school holidays, and for most of each summer, this institution was my "day-care center."

I am now a practicing urologist in Lompoc, California, and, in retrospect, I am sure that much of my motivation and tolerance for this geriatric-oriented specialty is derived from my contact with the "awakening" patients.

Most of the patients depicted in the movie were institutionalized for multiple sclerosis, cerebral palsy, parkinsonism, deviant behavior, senility (now Alzheimer's disease), and encephalitis. Many had relatively full mental capacity but were imprisoned in bodies that would not function in the real world.

My hours were spent sharing meals with patients and employees. I pushed wheelchairs when I was 9. I played dominoes and read numbers during weekly bingo games. I took piano lessons from a patient and played catch in one of the yards with some of the patients. I also heard stories of a New York that did not exist as I knew it.

Medicine today offers America's youth very little exposure to illness and disability that might motivate them into a medical career. I wish that more young people could interact with patients without the hazards of liability or fear of contagion. I think insight so gained would certainly motivate many more of them toward careers in medicine and allied fields.

One of my proudest moments at the institution was an awards ceremony in 1959, before I moved to Ohio, when all of the volunteers were given service awards, and I was granted my honorary Beth Abraham volunteer pin.

Oliver Sacks's vivid descriptions in his book and Penny Marshall's direction of the movie recapture the nature of this institution for the chronically ill. Somehow, between the lines and the camera images, I kept searching for a 9-year-old volunteer.

* * *

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JONATHAN E. RODNICK, MD
STEPHEN J. McPHEE, MD
Series' Editors

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Dr Reiner is in private practice in urology in Lompoc, California.

Reprint requests to Robert J. Reiner, MD, Diplomate American Board of Urology, Fellow American College of Surgeons, Ocean Ave Plaza, 1111 East Ocean Ave, Suite 3, Lompoc, CA 93436.

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Goetzl, Edward J.
Goldbloom, David S.
Golden, Jeffrey A.
Goldenberg, Don L.
Goldman, Mervin J.
Goldschlager, Nora F.
Goldsmith, Robert S.
Gomez, Gerardo A.
Goodstein, George
Gordin, Fred M.
Gostout, Christopher J.
Graffis, Linda
Granoff, Dan M.
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Greenspan, Francis S.
Griffin, Jerry C.
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Grosfeld, Jay L.
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Grumbach, Melvin M.
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Henderson, John C.
Herington, Thomas
Herman, John B.
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Hoffman, Richard E.
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Hollenberg, Milton
Holley, David R.
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Hopewell, Philip
Hopkins, David S.
Horner, Ronnie D.
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Howe, Roger K.
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Hughes, James P.
Hulley, Stephen B.
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Hummel, Linda
Hurt, Richard D.
Husson, Robert N.
Hutchins, Edwin B.

Illingworth, Roger

Jackson, Robert M.
Jacobs, Charlotte
Jacobs, Richard A.
Jaffe, Richard B.
Jagelman, David G.
Jamal, Ijazz
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Jenkins, Ronald D.
Jergesen, Harry E.
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Johns, Carol Johnson
Johnson, Herbert
Johnson, Joseph E. III
Johnson, Richard W., Jr
Jones, Robert
Jonsen, Albert R.
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Kagawan, Butch
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Schwartz, Seymour I.
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Young, Lowell S.

Zasler, Nathan
Zippin, Calvin
Ziring, Philip R.

Volume 155 INDEX July-December 1991

AUTHOR INDEX

Agnew, David C., Santa Barbara, Calif (Jul) 66
Alexander, Eben, Jr, Winston-Salem, NC (Oct) 430
Anders, Gregg T., Fort Sam Houston, Tex (Oct) 373
Ardalan, Bach, Miami, Fla (Aug) 176
Aslamy, Wazhma, Scottsdale, Ariz (Sep) 301

Bacon, George E., Grand Rapids, Mich (Oct) 428
Bailey, Steven R., Fort Sam Houston, Tex (Oct) 373
Baird, Robert, Orange, Calif (Aug) 171
Bal, Dileep G., Sacramento, Calif (Nov) 548
Baldwin, DeWitt C., Jr, Chicago, Ill (Aug) 140
Baringer, J. Richard, Salt Lake City, Utah (Nov) 528
Barnard, John A., Nashville, Tenn (Aug) 189
Bateman, J. Bronwyn, Los Angeles, Calif (Oct) 388
Beck, Anna C., Salt Lake City, Utah (Sep) 293
Benfield, John R., Sacramento, Calif (Oct) 407
Benjamin, Harold H., Santa Monica, Calif (Jul) 86
Berman, Arnold C., San Francisco, Calif (Oct) 415
Berman, Stephen, Denver, Colo (Dec) 649
Berrios, Daniel C., San Francisco, Calif (Aug) 133
Berry, Roy A., Sacramento, Calif (Nov) 531
Beuhler, Stephanie Pershing, Big Horn, Wyo (Nov) 504
Binder, Louis S., El Paso, Tex (Sep) 284
Bishai, David, Los Angeles, Calif (Oct) 429
Bishop, F. Marian, Salt Lake City, Utah (Oct) 426
Blanton, Herman M., Fort Sam Houston, Tex (Oct) 373
Blinder, Barton J., Newport Beach, Calif (Nov) 520
Bodenheimer, Thomas, San Francisco, Calif (Aug) 192
Boly, Lawrence R., San Francisco, Calif (Oct) 415
Borges, Mary L., Olympia, Wash (Dec) 613
Bosser, Sonya K., Bethesda, Md (Jul) 47
Boushey, Homer A., San Francisco, Calif (Jul) 72
Brosman, Stanley A., Santa Monica, Calif (Dec) 633
Burian, Pam, Los Angeles, Calif (Dec) 610
Burrow, Gerard N., La Jolla, Calif (Jul) 80
Bush, Thomas M., San Jose, Calif (Jul) 39

Caiozzo, Vince, Irvine, Calif (Aug) 169
Call, Gregory K., Salt Lake City, Utah (Jul) 70
Callaham, Michael, San Francisco, Calif (Sep) 289
Callister, Cyril Bruce, Salt Lake City, Utah (Sep) 299
Campofiori, Gail, Los Angeles, Calif (Oct) 416
Carroll, Peter R., San Francisco, Calif (Nov) 527
Carvalho, Paula G., Boise, Idaho (Nov) 525
Cash, Joseph M., Rapid City, SD (Dec) 644
Caudill, Timothy G., Reno, Nev (Sep) 292
Chappell, James A., Lubbock, Tex (Sep) 284
Chen, Valentina N., Stanford, Calif (Oct) 421
Chew, Chin Hin, Republic of Singapore (Aug) 186
Chin, Marshall H., Boston, Mass (Nov) 553
Church, Joseph A., Los Angeles, Calif (Nov) 547
Clever, Linda Hawes, San Francisco, Calif (Sep) 306, (Oct) 421, (Nov) 540
Coffey, Robert J., Nashville, Tenn (Aug) 189
Concepcion, Waldo, San Francisco, Calif (Nov) 494
Connolly, John P., Pensacola, Fla (Jul) 78
Conrad, Douglas J., San Francisco, Calif (Jul) 72
Coppola, Carl, Los Angeles, Calif (Aug) 193
Correa, Roy J., Jr, Seattle, Wash (Jul) 43
Cox, Ken, San Francisco, Calif (Nov) 494
Crade, Michael, Long Beach, Calif (Sep) 287
Craig, Timothy J., San Diego, Calif (Jul) 78
Crawford, Stephen W., Seattle, Wash (Nov) 488
Crooks, Catherine, San Diego, Calif (Nov) 548
Curtis, Jeffrey L., Ann Arbor, Mich (Jul) 72
Cutler, Robert W. P., Stanford, Calif (Oct) 421
Cuttitta, Frank, Bethesda, Md (Aug) 152

Daniels, George, Jr, Stanford, Calif (Dec) 634
Danielson, Kelvin, Scottsdale, Ariz (Sep) 301
Daugherty, Steven R., Chicago, Ill (Aug) 140
de Guzman, Nelson, Los Angeles, Calif (Dec) 610
Denny, Christopher, Los Angeles (Nov) 505
Dhar, Santi R., Brooklyn, NY (Aug) 181
Dieckmann, Ronald A., San Francisco, Calif (Sep) 287
Dor-Ner, Alexandra Dane, Boston, Mass (Nov) 555
Drakes, Thomas P., Redding, Calif (Jul) 76

Eckenfels, Edward J., Chicago, Ill (Aug) 140
Elder, John P., San Diego, Calif (Nov) 548
Emmons, Richard W., Berkeley, Calif (Aug) 136
Eng, Thomas R., Washington, DC (Dec) 613
Espina, Byron, Los Angeles (Dec) 610
Esquivel, Carlos O., San Francisco, Calif (Nov) 494
Evans, Gary W., Bemidji, Minn (Nov) 549

Farber, Debora B., Los Angeles, Calif (Oct) 388
Fedoruk, M Joseph, Anaheim, Calif (Dec) 663
Ferdman, Ronald M., Los Angeles, Calif (Nov) 547
Fink, Max, Stony Brook, NY (Nov) 515
Fischer, David J., Boise, Idaho (Oct) 410
Fogelson, David L., Santa Monica, Calif (Nov) 522
Friedman, Ira M., San Francisco, Calif (Aug) 136
Frost, Philip H., San Francisco, Calif (Oct) 424
Fye, Kenneth H., San Francisco, Calif (Dec) 642

Gadde, Hari, Brooklyn, NY (Oct) 419
Gardner, Vance O., Irvine, Calif (Aug) 169
Gasman, John D., Stanford, Calif (Oct) 412
Gelb, Alan, San Francisco, Calif (Sep) 289
Geller, Richard J., Fresno, Calif (Dec) 639
Gelpi, Armand P., Palo Alto, Calif (Sep) 260
Gerner, Robert, Los Angeles, Calif (Nov) 518
Gibbons, Harry L., Salt Lake City, Utah (Dec) 658
Gibbons, Robert P., Seattle, Wash (Jul) 43
Gilbert, Fred I., Jr, Honolulu, Hawaii (Jul) 61
Gitlin, Michael J., Los Angeles, Calif (Nov) 521
Golden, Alice M., Worcester, Mass (Oct) 384
Goldstein, Mary Kane, Palo Alto, Calif (Sep) 263
Goldstein, Michael S., Los Angeles, Calif (Jul) 86
Gordon, Gilad S., Seattle, Wash (Dec) 616
Grady, Deborah, San Francisco, Calif (Aug) 133
Gray, Gary M., Stanford, Calif (Dec) 660
Greer, Monte A., Portland, Ore (Jul) 83
Grimm, Susan, Denver, Colo (Dec) 649
Grindlinger, Howard M., Sacramento, Calif (Oct) 431

Haber, Richard J., San Francisco, Calif (Aug) 146
Halsted, Charles H., Davis, Calif (Dec) 605
Hamilton, Maurice E., Sacramento, Calif (Aug) 174
Hammond, Elizabeth H., Salt Lake City, Utah (Sep) 293
Hammons, Laura, Gallup, NM (Dec) 663
Harlan, John M., Seattle, Wash (Oct) 365
Harlin, Vivian K., Olympia, Wash (Dec) 613
Harris, Cheryl P., Salt Lake City, Utah (Nov) 528
Hebdon, C. Kent, Sandy, Utah (Dec) 658
Heckenlively, John R., Los Angeles, Calif (Oct) 388
Helfend, Lisa K., San Francisco, Calif (Jul) 72
Henderson, Vernon, Oakland, Calif (Sep) 253
Hendren, Robert L., Albuquerque, NM (Nov) 522
Hessel, Samuel J., Scottsdale, Ariz (Sep) 301
Hoch, Dana Frederich, San Jose, Calif (Nov) 551
Hoffman, Jerome R., Los Angeles, Calif (Sep) 290
Hori, Michael K., Sacramento, Calif (Nov) 525
Howard, P. Holbrook, Sacramento, Calif (Jul) 33
Howell, Lydia P., Sacramento, Calif (Jul) 33
Hung, Shaun S. J., Miami, Fla (Aug) 176
Hunter, Ripley H., San Francisco, Calif (Dec) 642

Imai, Kent, San Jose, Calif (Jul) 39

Jacobs, Michael B., Stanford, Calif (Aug) 178
Jamin, Denise, Los Angeles, Calif (Dec) 610
Janda, J. Michael, Berkeley, Calif (Oct) 421
Johnson, James E., Fort Sam Houston, Tex (Oct) 373
Johnson, Michael, Sacramento, Calif (Nov) 548

Kabalin, John N., Palo Alto, Calif (Dec) 632, 635
Kahn, Douglas, Newport Beach, Calif (Nov) 517
Kahn, Norman B., Davis, Calif (Dec) 653
Kane, John P., San Francisco, Calif (Oct) 424
Kanel, Gary, Los Angeles, Calif (Oct) 416
Karnes, William E., Rochester, Minn (Aug) 152
Karolewski, Alice N., Sacramento, Calif (Dec) 647
Kasdorf, Julia, Brooklyn, NY (Nov) 539

Katzman, Debra K., Stanford, Calif (Aug) 136
Kavanaugh, Anne, Crozet, Va (Oct) 369
Keeffe, Emmet B., Portland, Ore (Nov) 541
Keepers, George A., Portland, Ore (Nov) 516
Keesey, John C., Long Beach, Calif (Jul) 69
Kenney, Erin, San Diego, Calif (Nov) 548
Kingsley, Paul L., Ross, Calif (Jul) 87
Kirkman-Liff, Bradford L., Tempe, Ariz (Sep) 269
Kizer, Kenneth W., Davis, Calif (Oct) 430
Knight, Lawrence L., Boise, Idaho (Oct) 410, (Nov) 525
Kobayashi, John M., Seattle, Wash (Dec) 613
Koeffler, H. Phillip, Los Angeles, Calif (Nov) 505
Koenig, Kristi L., Orange, Calif (Oct) 400
Koo, John Y. M., San Francisco, Calif (Nov) 523
Korula, Jacob, Los Angeles, Calif (Oct) 416

Laine, Loren, Los Angeles, Calif (Sep) 274
Lane, Richard D., Tucson, Ariz (Nov) 521
Lardinois, Claude K., Reno, Nev (Sep) 292
Latham, Ricky D., Fort Sam Houston, Tex (Oct) 373
Lee, Loretta, Santa Ana, Calif (Dec) 663
Le Mauviel, Laurie, Minneapolis, Minn (Sep) 280
Levengood, Gary, San Francisco, Calif (Aug) 172
Levin, Barry, San Francisco, Calif (Nov) 494
Levine, Alexandra M., Los Angeles, Calif (Dec) 610
Levy, Jonathan M., Scottsdale, Ariz (Sep) 301
Lew, Chris, Honolulu, Hawaii (Jul) 61
Lewis, Janet, Los Altos, Calif (Jul) 38, (Aug) 194
Lewis, Jerry P., Sacramento, Calif (Nov) 531
Litt, Iris F., Stanford, Calif (Aug) 136
Loeb, John M., Castro Valley, Calif (Sep) 296
Lo Gerfo, James P., Seattle, Wash (Dec) 616
Lombard, Charles M., Mountain View, Calif (Sep) 296
Loosli, Alvin R., Walnut Creek, Calif (Aug) 191
Louie, Kevin W., San Francisco, Calif (Aug) 170
Lyons, Stephen, Moscow, Idaho (Dec) 620

McAllister, C. Kenneth, Fort Sam Houston, Tex (Oct) 373
McCormick, Frank, Emeryville, Calif (Nov) 505
MacFarlane, Michael T., Los Angeles, Calif (Dec) 634
Mackersie, Robert C., San Diego, Calif (Oct) 405
Malloy, Mary J., San Francisco, Calif (Oct) 424
Manfred, Freya, Bloomington, Minn (Dec) 615
Mann, Eberhard M., Honolulu, Hawaii (Nov) 520
Marcus, Robert, Palo Alto, Calif (Jul) 53
Marder, Richard A., Sacramento, Calif (Aug) 172
Marra, Christina, Seattle, Wash (Jul) 65
Mascola, Laurene, Los Angeles, Calif (Nov) 547
Meals, Roy A., Los Angeles, Calif (Aug) 170
Menninger, John A., Denver, Colo (Nov) 519
Merrell, Steven W., Rochester, Minn (Dec) 621
Meyer, Thomas J., Denver, Colo (Sep) 256
Miller, Scott R., Irvine, Calif (Oct) 404
Mitchell, Connie, Sacramento, Calif (Sep) 285
Montgomery, Terri, Los Angeles, Calif (Dec) 610
Mooney, Vert, San Diego, Calif (Aug) 173
Moore, Wesley S., Los Angeles, Calif (Oct) 407
Morris, James M., San Francisco, Calif (Aug) 172
Mower, William, Los Angeles, Calif (Sep) 290
Mueller, Juergen, Oakland, Calif (Oct) 400
Murdock, Margie A., Orange, Calif (Oct) 370
Murphey, William H., Portland, Ore (Oct) 423
Murray, Ronald S., Englewood, Colo (Jul) 68
Myers, Wayne, Hazard, Ky (Nov) 500
Myers, Woodrow A., Jr, New York, NY (Jul) 83

Nakazato, Paul, San Francisco, Calif (Nov) 494
Nambisan, Raman, Oakland, Calif (Sep) 253
Nathan, Julia, San Francisco, Calif (Sep) 290
Nesbitt, Thomas S., Davis, Calif (Dec) 653
Nichols, Peter, Los Angeles, Calif (Oct) 416
Nickens, Herbert W., Jr, Washington, DC (Jul) 27
Nightingale, Elena O., Washington, DC (Sep) 303
Nordyke, Robert A., Honolulu, Hawaii (Jul) 61
Norman, Lee A., Seattle, Wash (Oct) 413
Notkin, Herbert, Arcata, Calif (Jul) 86, (Aug) 191
Nudleman, Kenneth L., Orange, Calif (Jul) 67, 70
Nuwer, Marc R., Los Angeles, Calif (Jul) 67

Oboler, Sylvia K., Denver, Colo (Sep) 256
Odumakinde, Elizabeth A., Sacramento, Calif (Nov) 531
Olson, Kent R., San Francisco, Calif (Dec) 639
Organ, Claude H., Jr, Oakland, Calif (Sep) 253
Osborn, Robin E., San Diego, Calif (Jul) 78
O'Toole, David M., Worcester, Mass (Oct) 384

Padmanabhan, Krishnan, Brooklyn, NY (Aug) 181, (Oct) 419
Panacek, Edward A., Cleveland, Ohio (Sep) 286
Pane, Gregg A., Irvine, Calif (Sep) 285
Pascoe, Dennis C., Palo Alto, Calif (Sep) 263
Peck, Magda G., Omaha, Neb (Sep) 303
Poirier, Virginia C., Sacramento, Calif (Dec) 647
Presti, Joseph C., Jr, New York, NY (Nov) 527
Prochazka, Allan V., Denver, Colo (Sep) 256
Pultz, Constance, Charleston, SC (Oct) 432, (Nov) 537

Radany, Eric, San Francisco, Calif (Nov) 544
Raffin, Thomas A., Stanford, Calif (Sep) 307
Ramsey, Linda L., San Francisco, Calif (Aug) 183
Ramsey, Paul G., Seattle, Wash (Oct) 380
Rappaport, Maurice, San Jose, Calif (Nov) 516
Rarick, Mark U., Los Angeles, Calif (Dec) 610
Reed, Antoinette, Palo Alto, Calif (Jul) 46
Reiner, Robert J., Lompoc, Calif (Dec) 664
Rice, Charles L., Seattle, Wash (Oct) 365
Rickman, Leland S., San Diego, Calif (Jul) 47
Riley, Katherine, Seattle, Wash (Nov) 500
Rodrigo, Juan J., Sacramento, Calif (Aug) 169
Rose, Theodore, Oakland, Calif (Oct) 400
Rubin, Haya R., Baltimore, Md (Nov) 550
Russell, Liisa A., Sacramento, Calif (Jul) 33

Sabella, Joseph D., Napa, Calif (Oct) 428
Sageman, W. Scott, San Diego, Calif (Jul) 78
Sainsbury, Steven J., Templeton, Calif (Dec) 637
Salpeter, Shelley R., San Jose, Calif (Oct) 412
Salva, Paul S., Indianapolis, Ind (Oct) 428
Samlowski, Wolfram E., Salt Lake City, Utah (Sep) 293
Sanchez, Ramón M., San Diego, Calif (Jul) 78
Sandblom, Philip, Lausanne, Switzerland (Dec) 660
Sato, Judith K., Los Angeles, Calif (Nov) 547
Schachter, Julius, San Francisco, Calif (Aug) 136
Schaffenburg, Carlos A., Chevy Chase, Md (Sep) 312
Scherger, Joseph E., Davis, Calif (Aug) 191, (Dec) 653
Schmidt, Joseph D., San Diego, Calif (Dec) 633
Schneeweiss, Ronald, Seattle, Wash (Nov) 500
Schneider, Philip D., Sacramento, Calif (Dec) 621
Sefcik, Stephan E., Seattle, Wash (Dec) 616
Senécal, Pierre E., San Francisco, Calif (Dec) 639
Shapiro, Richard M., Stanford, Calif (Oct) 412
Shlotzhauer, Tammi L., San Jose, Calif (Jul) 39
Sibley, William A., Tucson, Ariz (Jul) 65
Silberman, Howard, Los Angeles, Calif (Oct) 405
Slife, David M., Fort Sam Houston, Tex (Oct) 373
Smith, Elizabeth Spencer, Santa Rosa, Calif (Jul) 82
Smith, Lloyd H., Jr, San Francisco, Calif (Sep) 306
Smith, Michael E., Oakland, Calif (Sep) 253
Sowa, Marian V., Long Beach, Calif (Jul) 64
Sparkes, Robert S., Los Angeles, Calif (Oct) 388
Stabile, Bruce E., San Diego, Calif (Oct) 408
Starkman, Elaine, Walnut Creek, Calif (Oct) 432
Stevens, Dennis L., Boise, Idaho (Nov) 525
Stewart, William B., San Francisco, Calif (Nov) 538
Stone, James, Stanford, Calif (Oct) 406
Sutton, Mark A., Seattle, Wash (Jul) 43
Sutton, Roger A. L., Vancouver, BC (Sep) 249
Szpakowski, Jean-Luc, Richmond, Calif (Nov) 494

Tang, Eddie, Los Angeles, Calif (Aug) 164
Tanji, Jeffrey L., Davis, Calif (Dec) 653
Teplitz, Raymond L., Sacramento, Calif (Jul) 33
Tipton, Ann C., Stanford, Calif (Aug) 136
Tompkins, Pendleton, San Mateo, Calif (Nov) 549
Truong, Daniel D., Orange, Calif (Jul) 69
Tucker, Elizabeth D., Salt Lake City, Utah (Sep) 299
Tunis, Sean, Baltimore, Md (Nov) 550
Tunzi, Marc, Twin Falls, Idaho (Nov) 548

Vallone, Robert P., Palo Alto, Calif (Sep) 263
Van Brunt, Edmund, Berkeley, Calif (Jul) 88
Vedder, Nicholas B., Seattle, Wash (Oct) 365
Velji, Anvar, Sacramento, Calif (Sep) 308
Vestal, Robert E., Boise, Idaho (Oct) 410
Volberding, Paul A., San Francisco, Calif (Nov) 540
Vora, Samir, Brooklyn, NY (Oct) 419

Wagner, Sheldon L., Corvallis, Ore. (Oct) 430
Walker, Ameae, Riverside, Calif. (Aug) 152
Walsh, John H., Los Angeles, Calif. (Aug) 152
Ward, John H., Salt Lake City, Utah (Sep) 293
Warnock, Martha L., San Francisco, Calif (Jul) 72
Wasserman, Stephanie, Denver, Colo (Dec) 649
Wasserstein, Philip H., Stanford, Calif. (Aug) 178
Waters, Cheryl H., Los Angeles, Calif. (Jul) 68
Watson, Craig, Sacramento, Calif. (Dec) 626
Waxman, Kenneth, Orange, Calif. (Oct) 370, 404
Weil, Thomas P., Asheville, NC (Nov) 538
Weiss, Eric, Woodside, Calif. (Sep) 288
Welch, Richard B., San Francisco, Calif (Aug) 172
Weleber, Richard G., Portland, Ore. (Oct) 423
Wenrich, Marjorie D., Seattle, Wash (Oct) 380
White, George L., Jr, Hattiesburg, Miss. (Sep) 299
Whitman, Neal A., Salt Lake City, Utah (Oct) 426
Williams, Hibbard E., Davis, Calif (Aug) 183
Winn, Robert K., Seattle, Wash (Oct) 365
Winograd, Carol Hutner, Palo Alto, Calif. (Sep) 263
Wise, Philip, San Diego, Calif (Dec) 635
Wong-Staal, Flossie, La Jolla, Calif (Nov) 481
Wood, Stephen Daniel, Salt Lake City, Utah (Sep) 299
Wray, Robert B., Salt Lake City, Utah (Sep) 293
Wu, Albert W., Baltimore, Md (Nov) 550
Wurlitzer, Fred, Burlingame, Calif (Oct) 429
Wyrebek, Michele, Sterling, Mass (Dec) 662

Yager, Joel, Los Angeles, Calif. (Nov) 523
Yang, Jack C., San Diego, Calif (Jul) 47
Yellin, Albert, Los Angeles, Calif (Oct) 416
Yeo, Kiat, Brooklyn, NY (Aug) 181
Yim, Kenneth K., Oakland, Calif (Sep) 253
Young, Russell L., San Diego, Calif. (Nov) 548

Zawada, Edward T., Jr, Sioux Falls, SD (Dec) 644
Zucconi, George, La Mesa, Calif (Dec) 664

IN MEMORIAM

California Medical Association:

Adams, Deane T., Jun 30, 1991 (Sep) 222
Aycinena, Juan, Jul 6, 1991 (Nov) 461
Baker, Stephen T., May 19, 1991 (Aug) 109
Banta, Edwin, Jr, Apr 3, 1991 (Aug) 109
Barnett, Clair B., Sep 1, 1991 (Nov) 461
Bartlett, John C., Jun 13, 1991 (Nov) 461
Batten, Douglas H., Aug 14, 1991 (Nov) 461
Berner, Richard A., Jun 10, 1991 (Sep) 222
Bertero, Jules, Apr 19, 1991 (Nov) 461
Bescoby, Felix J., Jul 11, 1991 (Nov) 461
Blaufuss, Arnold, May 5, 1991 (Aug) 109
Boomer, Joseph M., May 12, 1991 (Nov) 461
Borkovic, Steven P., Mar 27, 1991 (Aug) 109
Bramham, James C., Mar 17, 1991 (Aug) 109
Cable, Sheldon, Mar 20, 1991 (Aug) 109
Callahan, Rosemarie, Jun 13, 1991 (Sep) 222
Calvy, William J., Sep 1991 (Nov) 461
Campion, Gwendolyn, May 9, 1991 (Aug) 109
Casberg, Melvin A., Mar 27, 1991 (Sep) 222
Chandler, Arthur L., Apr 23, 1991 (Nov) 461
Chennell, Bruce A., Mar 30, 1991 (Sep) 222
Cronenwett, Paul H., Apr 25, 1991 (Aug) 109
Dakin, Richard L., Mar 3, 1991 (Aug) 109
Dowdy, Kemp, Aug 11, 1991 (Nov) 461
Draper, Oliver D., Apr 13, 1991 (Sep) 222
Drapkin, Harold, Apr 30, 1991 (Aug) 109
Edwards, Bob, Jul 12, 1991 (Aug) 117
Fitch, William M., Mar 9, 1991 (Aug) 109
Florin, Alvin C., Jul 29, 1991 (Nov) 461
Foley, Robert D., Jun 8, 1991 (Sep) 222
Gerlach, Richard D., Jun 27, 1991 (Sep) 222
Giberson, A. F., May 5, 1991 (Aug) 109
Gibson, George C., Apr 18, 1991 (Aug) 109
Gilmore, William M., Jul 11, 1991 (Nov) 461
Ginsberg, Robert L., May 22, 1991 (Aug) 109
Goodson, Samuel B., Jan 21, 1991 (Sep) 222
Gould, Lloyd E., Sep 9, 1991 (Nov) 461
Gray, Richard, Apr 28, 1991 (Aug) 109
Greenlaw, Colin T., Jun 16, 1991 (Sep) 222
Gull, Reuben, Apr 21, 1991 (Nov) 461
Hack, Rudolf W., Jul 10, 1991 (Sep) 222
Hamilton, James J., Apr 11, 1991 (Aug) 109
Hanigan, Thomas E., Apr 1991 (Aug) 109
Hartzman, Robert, Jun 20, 1991 (Nov) 461
Haskins, George W., Feb 19, 1991 (Aug) 109
Hastings, Orville L., Jan 30, 1991 (Aug) 109
Hawk, Walter D., Jul 21, 1991 (Nov) 461
Hayes, Donald Murray, Aug 17, 1991 (Nov) 461
Huffer, Richard L., May 18, 1991 (Aug) 109
Humber, John Davis, May 20, 1991 (Aug) 109
Johnson, Allen R., May 1, 1991 (Sep) 222
Johnson, David A., Jul 27, 1991 (Nov) 461
Jules, Philip, Mar 28, 1991 (Aug) 109
Klein, Russell R., Apr 1, 1991 (Aug) 109
Koch, Fremont P., Sep 27, 1991 (Nov) 461
Lane, Robert D., May 15, 1991 (Aug) 109
Leonard, Carl D., May 24, 1991 (Aug) 109
Lewis, William B., Jr, Mar 14, 1991 (Aug) 109
McCarty, Kevin, Aug 8, 1991 (Nov) 461
McPharlin, James H., Apr 20, 1991 (Aug) 109
McPherson, Alan Given, May 10, 1991 (Nov) 461
Martin, Frank H., Mar 12, 1991 (Aug) 117
Mason, Charles E., Apr 9, 1991 (Sep) 222
Massengill, James B., Jul 1, 1991 (Nov) 461
Matychowiak, Francis A., May 25, 1991 (Aug) 117
Maxson, Eugene S., Apr 23, 1991 (Aug) 117
Meador, James H., Sep 1, 1991 (Nov) 463
Menda, Kishen B., Jul 11, 1991 (Nov) 463
Merrill, Robert L., Aug 31, 1991 (Nov) 463
Miller, Earl M., Mar 27, 1991 (Aug) 117
Milton, James T., Mar 12, 1991 (Aug) 117
Moffitt, Laurl W., May 25, 1991 (Sep) 222
Momary, Hassan M., Mar 29, 1991 (Aug) 117
Mootoo, Siegfried A., Apr 10, 1991 (Aug) 117
Mosso, James A., Mar 23, 1991 (Aug) 117
Nemeth, Laslo Jeno, Apr 24, 1991 (Aug) 117
Nesselrod, Jerrold Peerman, Sep 6, 1991 (Nov) 461
Nudelman, Howard Lee, Jul 1, 1991 (Sep) 222
Olmstead, Luke R., Feb 9, 1991 (Sep) 222
Paxson, Jane T., May 1, 1991 (Sep) 222
Peck, Samuel G., Sep 1, 1991 (Nov) 463
Phillips, R. E., Jul 19, 1991 (Nov) 463
Potter, George V., Jul 13, 1991 (Nov) 463
Ray, Leighton W., Jul 28, 1991 (Nov) 463
Richmond, Robert A., Aug 18, 1991 (Nov) 463
Rixford, Henry C., May 13, 1991 (Aug) 117
Robertson, Helen R., Mar 12, 1991 (Aug) 117
Robley, Wendell W., May 21, 1991 (Sep) 222
Rubens, Mark Kenneth, May 1991 (Sep) 222
Rydell, John R., May 13, 1991 (Aug) 117
Schmela, Woodrow W., May 28, 1991 (Sep) 222
Sokhos, Dimitri, Apr 21, 1991 (Aug) 117
Spaur, R. Craig, Jun 8, 1991 (Nov) 463
Splithoff, Clarence A., Jun 17, 1991 (Sep) 222
Strange, Gerald, Mar 5, 1991 (Aug) 117
Taboada, Jose, May 6, 1991 (Aug) 117
Terry, Howard R., Mar 29, 1991 (Aug) 117
Wade, Robert M., Apr 30, 1991 (Aug) 117
Waldron, Melvin C., Jan 13, 1991 (Sep) 222
Walter, Norman T., Mar 28, 1991 (Aug) 117
Weiler, Philip G., Jun 14, 1991 (Sep) 222
White, Edward D., Jun 2, 1991 (Sep) 222
Wood, Paul E., Apr 1991 (Aug) 117
Woodruff, Nathan H., Jr, Apr 25, 1991 (Aug) 117
Zeigler, Paul, Mar 1991 (Aug) 117

Denver Medical Society:

Blaney, Loren F., Aug 14, 1991 (Nov) 463
Hannum, John N., Apr 19, 1991 (Aug) 117
Lubchenco, Michael A., Aug 11, 1991 (Nov) 463
Meister, Edward J., Apr 28, 1991 (Aug) 117
Musman, David J., Jun 17, 1991 (Sep) 222
Schonebaum, Robert M., Jul 17, 1991 (Nov) 463

Idaho Medical Association:

Goates, Gregory L., Jul 26, 1991 (Nov) 463
Wehler, Andrew J., Aug 26, 1991 (Nov) 463

New Mexico Medical Society:

Blake, Henry W., Jun 23, 1991 (Sep) 222
Farid, Sada, Mar 1991 (Sep) 222
Gutowski, Franz, Aug 4, 1991 (Nov) 463
Smith, George L., Jun 12, 1991 (Sep) 222
Spining, William D., Jun 23, 1991 (Nov) 463

SUBJECT INDEX

A

Abortion 'Gag' Rule (Correspondence),
Herbert Notkin . . . . . (Aug) 191
Laura Hammons . . . . . (Dec) 663
Acid-Base Disorders, see *Practical Approach to*
Acute Mediastinal Widening Following Endotracheal Intubation and Gastric Lavage (Radiologic Case), Krishnan Padmanabhan, Hari Gadde, Samir Vora . . . . . (Oct) 419
[AIDS], see *Cardiac Dysfunction in Patients Seropositive for the Human Immunodeficiency Virus*
The AIDS Virus—What We Know and What We Can Do About It (Biomedical Science), Flossie Wong-Staal . . . . . (Nov) 481
Alcohol, see *Menace of*
Amnesiac, see *Memoirs of an*
Angiographic Yield in Penetrating Extremity Trauma, Vernon Henderson, Raman Nambisan, Michael E. Smith, Kenneth K. Yim, Claude H. Organ, Jr. . . . . (Sep) 253
Animal Rights and Animal Experimentation—Implications for Physicians, Armand P. Gelpi . . . . . (Sep) 260
Editorial, Thomas A. Raffin . . . . . (Sep) 307
Anti-inflammatory Drugs—Proposed Guidelines for Monitoring Toxicity, see *Nonsteroidal*
Antiphospholipid Syndrome, see *Superior Mesenteric Artery Thrombosis Associated With*
Arizona, see *Public Perceptions of Health Care Problems—An Analysis From*
Aspergillar Myocarditis and Acute Coronary Artery Occlusion in an Immunocompromised Patient, Michael K. Hori, Lawrence L. Knight, Paula G. Carvalho, Dennis L. Stevens . . . . . (Nov) 525
Autocrine Growth Factors and Solid Tumor Malignancy (Conferences and Reviews), Moderator: John H. Walsh; Discussants: William E. Karnes, Frank Cuttitta, Ameae Walker . . . . . (Aug) 152
Editorial, Robert J. Coffey, John A. Barnard . . . . . (Aug) 189

B

Betamix, see *Toxic Exposure to*
Bilateral Spontaneous Renal Hemorrhage Due to Polyarteritis Nodosa, Joseph C. Presti, Jr, Peter R. Carroll . . . . . (Nov) 527

Biomedical Science:

The AIDS Virus—What We Know and What We Can Do About It, Flossie Wong-Staal . . . . . (Nov) 481
Causes and Prevention of Calcium-containing Renal Calculi, Roger A. L. Sutton . . . . . (Sep) 249
Editorial, Lloyd H. Smith, Jr . . . . . (Sep) 306
Intravenous Immune Globulin Use in Patients With Human Immunodeficiency Virus-Related Thrombocytopenia Who Need Dental Extraction, Mark U. Rarick, Pam Burian, Nelson de Guzman, Byron Espina, Terri Montgomery, Denise Jamin, Alexandra M. Levine . . . . . (Dec) 610
Jejunal Brush-Border Folate Hydrolase—A Novel Enzyme, Charles H. Halsted . . . . . (Dec) 605
Editorial, Gary M. Gray . . . . . (Dec) 660
Mechanisms and Consequences of Leukocyte-Endothelial Interaction, John M. Harlan, Nicholas B. Vedder, Robert K. Winn, Charles L. Rice . . . . . (Oct) 365

Biopsy of Superficial Masses in Children, see *Fine Needle Aspiration*
Bismuth Subsalicylate, see *Fatal Salicylate Toxicity From*
Border Health, see *Partnerships for Improving*
Bowel Obstruction Due to Newly Diagnosed Inoperable Advanced Ovarian Cancer With Medical Therapy, see *Resolution of*
Boy With Neck Pain After Motor-Vehicle Accident, see *3-Year-Old*
Brain Cancer, see *Memoirs of an Amnesiac—Two Years With*
Breast, see *Sarcoidosis of the*

C

Calcium-containing Renal Calculi, see *Causes and Prevention of*
Calf Deep Venous Thrombosis, see *Home Treatment of*
California Primary Care Physicians, see *Smoking Cessation Attitudes, Practices, and Policies Among*
Cancer, see *Molecular Mechanisms of*
Cancer, see *Numb Chin in Metastatic*
Cancer Patients and Support Groups (Correspondence), Harold H. Benjamin, Michael S. Goldstein . . . . . (Jul) 86
Cancer Patients for Rehabilitation Potential, see *Evaluating*
Cardiac Dysfunction in Patients Seropositive for the Human Immunodeficiency Virus, James E. Johnson, David M. Slife, Gregg T. Anders, Steven R. Bailey, Herman M. Blanton, C. Kenneth McAllister, Ricky D. Latham . . . . . (Oct) 373
Cardiac Tamponade, and Cutaneous Vasculitis, see *Idiopathic Mediastinitis With Superior Vena Cava Obstruction,*
Cardiomyopathy Associated With High-Dose Interleukin-2 Therapy, Anna C. Beck, John H. Ward, Elizabeth H. Hammond, Robert B. Wray, Wolfram E. Samlowski . . . . . (Sep) 293
Causes and Prevention of Calcium-containing Renal Calculi (Biomedical Science), Roger A. L. Sutton . . . . . (Sep) 249
Editorial, Lloyd H. Smith, Jr . . . . . (Sep) 306
Central Nervous System, see *Sarcoidosis of*
Central Nervous System Sarcoidosis, see *Intractable Hiccups as a Presentation of*
Charges for Comprehensive Obstetric Care at Teaching and Nonteaching Hospitals—A Comparison, Gilad S. Gordon, Stephan E. Sefcik, James P. Lo Gerfo . . . . . (Dec) 616
Children Who Received Transfusions in Mexico, see *Human Immunodeficiency Virus Infection in*
Chin, see *Numb*
Chlamydia Pneumoniae Lower Respiratory Tract Infections Among University Students in Northern California, see *Incidence of*
Ciguatera Fish Poisoning in San Francisco, California, Caused by Imported Barracuda, Richard J. Geller, Kent R. Olson, Pierre E. Senécal . . . . . (Dec) 639
Ciliary Dyskinesia, see *Primary*
Cisplatin Therapy-Associated Recurrent Toxic Shock Syndrome, Arnold C. Berman, Lawrence R. Boly . . . . . (Oct) 415
Clinical Diagnosis of Splenomegaly (Conferences and Reviews), Jack C. Yang, Leland S. Rickman, Sonya K. Bosser . . . . . (Jul) 47
Colorado Pediatricians and Family Physicians in the Medicaid Program, see *Participation of*

Commentary:

Managed-Care Plans—Their Future Under National Health Insurance, Thomas P. Weil . . . . . (Nov) 533
Medical Education, Training, and Health Care Services in the Republic of Singapore, Chin Hin Chew . . . . . (Aug) 186
Partnerships for Improving Border Health, Elena O. Nightingale, Magda G. Peck . . . . . (Sep) 303
Editorial, Linda Hawes Clever . . . . . (Sep) 306
Perils of Providing Medical Opinion—A State Medical Association's Experience, Hibbard E. Williams, Linda L. Ramsey . . . . . (Aug) 183
Physician, Heal Thy Planet, William B. Stewart . . . . . (Nov) 538
Teething as a Cause of Death—A Historical Review, Harry L. Gibbons, C. Kent Hebdon . . . . . (Dec) 658
Trial and Tribulation of Egerton Yorrick Davis, Gerard N. Burrow . . . . . (Jul) 80

Concerned Patient (Lessons From the Practice), Edmund Van Brunt . . . . . (Jul) 88

Conferences and Reviews:

Autocrine Growth Factors and Solid Tumor Malignancy, Moderator: John H. Walsh; Discussants: William E. Karnes, Frank Cuttitta, Ameae Walker . . . . . (Aug) 152
Editorial, Robert J. Coffey, John A. Barnard . . . . . (Aug) 189
Clinical Diagnosis of Splenomegaly, Jack C. Yang, Leland S. Rickman, Sonya K. Bosser . . . . . (Jul) 47
Hemobilia—Evolution of Current Diagnosis and Treatment, Steven W. Merrell, Philip D. Schneider . . . . . (Dec) 621
Editorial, Philip Sandblom . . . . . (Dec) 660
Hepatitis C Virus—A Review, Eddie Tang . . . . . (Aug) 164
Molecular Genetics of Retinitis Pigmentosa, Moderator: Debora B. Farber; Discussants: John R. Heckenlively, Robert S. Sparkes, J. Bronwyn Bateman . . . . . (Oct) 388

Editorial, Richard G. Weleber, William H. Murphey . . . (Oct) 423
Molecular Mechanisms of Cancer, Moderator: H. Phillip Koeffler; Discussants: Frank McCormick, Christopher Denny . . . . . (Nov) 505
Editorial, Eric H. Radany . . . . . (Nov) 544
Painful Subacute Thyroiditis in Hawaii, Robert A. Nordyke, Fred I. Gilbert, Jr, Chris Lew . . . . . (Jul) 61
Editorial, Monte A. Greer . . . . . (Jul) 83
Practical Approach to Acid-Base Disorders, Discussant: Richard J. Haber . . . . . (Aug) 146
Primary Ciliary Dyskinesia, Laurie Le Mauviel . . . . . (Sep) 280
Status Epilepticus—Clinical Features, Pathophysiology, and Treatment, Craig Watson . . . . . (Dec) 626
Understanding Osteoporosis, Robert Marcus . . . . . (Jul) 53
Upper Gastrointestinal Tract Hemorrhage, Discussant: Loren Laine . . . . . (Sep) 274
Vibrio vulnificus—Hazard on the Half Shell, Kristi L. Koenig, Juergen Mueller, Theodore Rose . . . . . (Oct) 400
Editorial, J. Michael Janda . . . . . (Oct) 421

Coronary Artery Occlusion, see *Aspergillar Myocarditis and Acute*

Correspondence:

Abortion 'Gag' Rule, Herbert Notkin . . . . . (Aug) 191
Laura Hammons . . . . . (Dec) 663
Cancer Patients and Support Groups, Harold H. Benjamin, Michael S. Goldstein . . . . . (Jul) 86
The Digital Rectal Examination in Women, Pendleton Tompkins . . . . . (Nov) 549
Do We Need Warning Labels on Food?, Alvin R. Loosli . . . . (Aug) 191
Joseph E. Scherger . . . . . (Aug) 191
Reply, Thomas Bodenheimer . . . . . (Aug) 192
Human Immunodeficiency Virus Infection in Children Who Received Transfusions in Mexico, Ronald M. Ferdman, Joseph A. Church, Laurene Mascola, Judith K. Sato . . . . . (Nov) 547
Inexpensive, Convenient Adjunct for the Treatment of Diabetes, Gary W. Evans . . . . . (Nov) 549
Medical Tourists, David Bishai . . . . . (Oct) 429
Reply, Fred Wurlitzer . . . . . (Oct) 429
Menace of Alcohol, Eben Alexander, Jr . . . . . (Oct) 430
Reply, Kenneth W. Kizer . . . . . (Oct) 430
Perspectives on 'Impairment,' Sheldon L. Wagner . . . . . (Oct) 430
Positive Preemployment Urine Drug Screen Caused by Foreign-Manufactured Vitamin Formulation, M. Joseph Fedoruk, Loretta Lee . . . . . (Dec) 663
Public Interest in Human Growth Hormone Therapy, Paul S. Salva, George E. Bacon . . . . . (Oct) 428
Redwood Medicare Assignment Program, Herbert Notkin . . . . (Jul) 86
Smoking Cessation Attitudes, Practices, and Policies Among California Primary Care Physicians, Russell L. Young, Catherine Crooks, John P. Elder, Erin Kenney, Dileep G. Bal, Michael Johnson . . . . . (Nov) 548
Tort Reform Works, Joseph D. Sabella . . . . . (Oct) 428
Toxic Exposure to Betamix, Marc Tunzi . . . . . (Nov) 548
The Value of Defiance, Howard M. Grindlinger . . . . . (Oct) 431
WARNING—Inhaling Tabasco Products Can Be Hazardous to Your Health, Haya R. Rubin, Albert W. Wu, Sean Tunis . . . . . (Nov) 550

D

Decision Making in Critically Ill Patients With Hematologic Malignancy, Stephen W. Crawford . . . . . (Nov) 488
Deep Venous Thrombosis, see *Home Treatment of Calf*
Dental Extraction, see *Intravenous Immune Globulin Use in Patients With Human Immunodeficiency Virus-Related Thrombocytopenia Who Need*
Desperately Seeking Primary Prevention (Lessons From the Practice), Anonymous . . . . . (Sep) 310
Diabetes, see *Inexpensive, Convenient Adjunct for the Treatment of*
Dietary Folate—The Digestible Vitamin (Editorial), Gary M. Gray . . . . . (Dec) 660
Domestic Violence—Risk Factors and Outcomes, Daniel C. Berrios, Deborah Grady . . . . . (Aug) 133
Do We Need Warning Labels on Food? (Correspondence), Alvin R. Loosli . . . . . (Aug) 191
Joseph E. Scherger . . . . . (Aug) 191
Reply, Thomas Bodenheimer . . . . . (Aug) 192
Drug Screen Caused by Foreign-Manufactured Vitamin Formulation, see *Positive Preemployment Urine*
Durable Power of Attorney for Health Care—Are We Ready for It?, Mary Kane Goldstein, Robert P. Vallone, Dennis C. Pascoe, Carol Hutner Winograd . . . . . (Sep) 263
Dyskinesia, see *Primary Ciliary*

E

Editorials:

Border Health Spans the Continent, Linda Hawes Clever . . . . (Sep) 306
Dietary Folate—The Digestible Vitamin, Gary M. Gray . . . . . (Dec) 660
How We Get Stoned, Lloyd H. Smith, Jr . . . . . (Sep) 306
International Health, Anvar Velji . . . . . (Sep) 308
Lethal Leviathan—*Vibrio vulnificus*, J. Michael Janda . . . . . (Oct) 421
Liver Transplantations—Challenges for the Future, Emmet B. Keeffe . . . . . (Nov) 541
Medical Student Section, Valentina N. Chen, Robert W. P. Cutler . . . . . (Oct) 421
Molecular Advances in Retinitis Pigmentosa, Richard G. Weleber, William H. Murphey . . . . . (Oct) 423
Molecular Genetics in the Cancer Clinic, Eric Radany . . . . . (Nov) 544
More Great News for Readers . . . . . (Oct) 421
Niacin—The Long and the Short of It, Mary J. Malloy, Philip H. Frost, John P. Kane . . . . . (Oct) 424
Physicians and Animal Experimentation, Thomas A. Raffin . . (Sep) 307
Physicians and the Human Immunodeficiency Virus, Paul A. Volberding . . . . . (Nov) 540
Preceptorships in the 21st Century—The Return of the Apprentice, F. Marian Bishop, Neal A. Whitman . . . . . (Oct) 426
Subacute Thyroiditis, Monte A. Greer . . . . . (Jul) 83
There's a Long, Long Trail A-winding . . . . . (Nov) 540
Two Medical Worlds—Separate and Unequal, Woodrow A. Myers, Jr . . . . . (Jul) 83
Understanding Autocrine Growth Regulation, Robert J. Coffey, John A. Barnard . . . . . (Aug) 189
Why Should Every Physician Know About Hemobilia?, Philip Sandblom . . . . . (Dec) 660

Egerton Yorrick Davis, see *Trial and Tribulation of*
Emergency Medicine, see *Epitomes*
Endotracheal Intubation and Gastric Lavage, see *Acute Mediastinal Widening Following*
Epilepticus, see *Status*

Epitomes:

Emergency Medicine:

Zidovudine for Prophylaxis of Human Immunodeficiency Virus Infection After Accidental Exposure, Louis S. Binder, James A. Chappell . . . . . (Sep) 284
Magnesium and Acute Myocardial Infarction, Connie Mitchell . . . . . (Sep) 285
Preventing and Controlling Violence in Emergency Departments, Gregg A. Pane . . . . . (Sep) 285
Neuromuscular Blockage in Emergency Medicine, Edward A. Panacek . . . . . (Sep) 286
Transvaginal Imaging of Ectopic Pregnancy, Michael Crade . . (Sep) 287
Rectal Diazepam Therapy for Prehospital Pediatric Status Epilepticus, Ronald A. Dieckmann . . . . . (Sep) 287
Bacterial Meningitis in Emergency Departments, Eric Weiss . . . . . (Sep) 288
Human Immunodeficiency Virus Precautions in Emergency Departments, Alan Gelb . . . . . (Sep) 289
High-Dose Epinephrine in Cardiac Arrest, Michael Callaham (Sep) 289
When to Image Cervical Spine Injuries, Jerome R. Hoffman, William Mower . . . . . (Sep) 290
Terminating Paroxysmal Supraventricular Tachycardias With Adenosine, Julia Nathan . . . . . (Sep) 290

General Surgery:

Advances in the Management of Hemorrhagic Shock, Scott R. Miller, Kenneth Waxman . . . . . (Oct) 404
Use and Abuse of Parenteral Nutrition, Howard Silberman . . . (Oct) 405
Procuring Donor Organs for Transplantation, Robert C. Mackersie . . . . . (Oct) 405

Surgical Treatment of Chronic Ulcerative Colitis, James Stone . . . (Oct) 406
Efficacy of Carotid Endarterectomy in Randomized Trials, Wesley S. Moore . . . (Oct) 407
Surgical Treatment of Hemoptysis, John R. Benfield . . . (Oct) 407
Laparoscopic Cholecystectomy, Bruce E. Stabile . . . (Oct) 408

Neurology:
Use of Antiepileptic Drugs in Pregnancy, Marian V. Sowa . . . (Jul) 64
Human T-cell Leukemia Virus Myelopathy, William A. Sibley (Jul) 65
Acquired Immunodeficiency Syndrome Dementia, Christina Marra . . . (Jul) 65
Treatment of Cluster Headaches, David C. Agnew . . . (Jul) 66
Electroencephalographic Brain Mapping, Marc R. Nuwer . . . (Jul) 67
Transcranial Doppler Study, Kenneth L. Nudleman . . . (Jul) 67
Myth of the Chronic Fatigue Syndrome, Ronald S. Murray . . . (Jul) 68
Selegiline (Eldepryl) for Parkinson's Disease, Cheryl H. Waters . . . (Jul) 68
Intravenous γ-Globulin for Chronic Inflammatory Demyelinating Polyneuropathy and Myasthenia Gravis, John D. Keesey . . . (Jul) 69
Botulinum Toxin Therapy, Daniel D. Truong . . . (Jul) 69
Preventing Chemotherapy-induced Neuropathy, Kenneth L. Nudleman . . . (Jul) 70
Carotid Endarterectomy, Gregory K. Call . . . (Jul) 70

Orthopedics:
Tissue Banking, Juan J. Rodrigo . . . (Aug) 169
Medical Management of Spinal Cord Injury, Vance O. Gardner, Vince Caiozzo . . . (Aug) 169
Ilizarov Method, Kevin W. Louie . . . (Aug) 170
Update on the Diagnosis and Treatment of Scaphoid Fractures, Roy A. Meals . . . (Aug) 170
Open Reduction of Pelvic Fractures, Robert Baird . . . (Aug) 171
Bearing Surfaces in Total Joint Replacement, Richard B. Welch, Gary Levengood . . . (Aug) 172
Arthroscopic-Assisted Reconstruction of the Anterior Cruciate Ligament, Richard A. Marder . . . (Aug) 172
Percutaneous Discectomy, James M. Morris . . . (Aug) 172
Objective Measurements for Rehabilitation After Back Injury, Vert Mooney . . . (Aug) 173

Psychiatry:
Electroconvulsive Therapy, Max Fine . . . (Nov) 515
Electrophysiologic Evaluation for Brain Dysfunction, Maurice Rappaport . . . (Nov) 516
Prophylaxis of Antipsychotic Drug-Induced Extrapyramidal Syndromes, George A. Keepers . . . (Nov) 516
Panic Disorder, Douglas Kahn . . . (Nov) 517
Rational Polydrug Use in Psychiatry, Robert Gerner . . . (Nov) 518
Tobacco Dependence and Smoke-free Psychiatric Units, John A. Menninger . . . (Nov) 519
Eating Disorders in Psychiatric Illness, Barton J. Blinder . . . (Nov) 519
Nocturnal Enuresis, Eberhard M. Mann . . . (Nov) 520
Treatment-Resistant Depression, Michael J. Gitlin . . . (Nov) 521
Antidepressant Treatment in Patients With Heart Disease, Richard D. Lane . . . (Nov) 521
Obsessive-Compulsive Disorder, David L. Fogelson . . . (Nov) 522
Brain Imaging and Neurodevelopmental Psychiatry, Robert L. Hendren . . . (Nov) 522
Treating Compulsive Behaviors in Dermatology, John Y. M. Koo . . . (Nov) 523
Bulimia Nervosa, Joel Yager . . . (Nov) 523

Urology:
Prostate-Specific Antigen, John N. Kabalin . . . (Dec) 632
BCG Vaccine in Urinary Bladder Cancer, Stanley A. Brosman . . . (Dec) 633
Medical Treatment of Benign Prostatic Hyperplasia, Joseph D. Schmidt . . . (Dec) 633
Screening for Prostate Cancer, Michael T. MacFarlane . . . (Dec) 634
Laparoscopy in Urology, George Daniels, Jr . . . (Dec) 634
Extracorporeal Shock-Wave Lithotripsy With Minimal or No Anesthesia, John N. Kabalin . . . (Dec) 635
Male Infertility Update, Philip Wise . . . (Dec) 635

Evaluating Cancer Patients for Rehabilitation Potential, David M. O'Toole, Alice M. Golden . . . (Oct) 384
Exocrine Glands, see *Sarcoidosis of the Breast, Central Nervous System, and*
Experimentation—Implications for Physicians, see *Animal Rights and Animal*

F

Family Physicians, see *Obstetric Care, Medicaid, and*
Fatal Salicylate Toxicity From Bismuth Subsalicylate, Steven J. Sainsbury . . . (Dec) 637
Fever of Unknown Origin, see *Gastric Tuberculosis Presenting as*
Fine Needle Aspiration Biopsy of Superficial Masses in Children, Lydia Pleotis Howell, Liisa A. Russell, P. Holbrook Howard, Raymond L. Teplitz . . . (Jul) 33
Folate, see *Dietary*
Food, see *Do We Need Warning Labels on*
Fulminant Hepatic Failure Following Low-Dose Sustained-Release Niacin Therapy in Hospital, David J. Fischer, Lawrence L. Knight, Robert E. Vestal . . . (Oct) 410
Editorial, Mary J. Malloy, Philip H. Frost, John P. Kane . . (Oct) 424

G

Gastric Lavage, see *Acute Mediastinal Widening Following Endotracheal Intubation and*
Gastric Tuberculosis Presenting as Fever of Unknown Origin, Shelley R. Salpeter, Richard M. Shapiro, John D. Gasman (Oct) 412
Gastrointestinal Tract Hemorrhage, see *Upper*
General Surgery, see *Epitomes*
Genetics of Retinitis Pigmentosa, see *Molecular*

H

Headache, see *Spontaneous Intracranial Hypotension—An Uncommon and Underrecognized Cause of*
[Health Care], see *Two Medical Worlds—Separate and Unequal*
Health Care Problems—An Analysis From Arizona, see *Public Perceptions of*
Health Status of Minority Populations in the United States, Herbert W. Nickens . . . (Jul) 27
Editorial, Woodrow A. Myers, Jr . . . (Jul) 83
Heart and Mind (Lessons From the Practice), Marshall H. Chin . . . (Nov) 553
Helmet Use Improves Outcomes After Motorcycle Accidents, Margie A. Murdock, Kenneth Waxman . . . (Oct) 370
Hematologic Malignancy, see *Decision Making in Critically Ill Patients With*
Hemobilia—Evolution of Current Diagnosis and Treatment (Conferences and Reviews), Steven W. Merrell, Philip D. Schneider . . . (Dec) 621
Editorial, Philip D. Sandblom . . . (Dec) 660
[Hemochromatosis], see Vibrio vulnificus—*Hazard on the Half Shell*
Hemodialysis, see *Isoniazid Overdose—Successful Treatment with Pyridoxine and*
Hemoptysis in a Patient With Tuberculosis, see *Lung Mass and*
Hemorrhage, see *Upper Gastrointestinal Tract*
Hepatic Failure Following Low-Dose Sustained-Release Niacin Therapy in Hospital, see *Fulminant*
Hepatitis B, see *Screening for . . . During Pregnancy*
Hepatitis C Virus—A Review (Conferences and Reviews), Eddie Tang . . . (Aug) 164
Hepatocellular Carcinoma Coexisting With Hepatic Adenoma—Incidental Discovery After Long-Term Oral Contraceptive Use, Jacob Korula, Albert Yellin, Gary Kanel, Gail Campofiori, Peter Nichols . . . (Oct) 416
Hiccups as a Presentation of Central Nervous System Sarcoidosis, see *Intractable*
Home Treatment of Calf Deep Venous Thrombosis, Cyril Bruce Calliser, Stephen Daniel Wood, George L. White, Jr, Elizabeth D. Tucker . . . (Sep) 299
How We Get Stoned (Editorial), Lloyd H. Smith, Jr . . . (Sep) 306
Human Growth Hormone Therapy, see *Public Interest in*
Human Immunodeficiency Virus, see *Cardiac Dysfunction in Patients Seropositive for the*

Human Immunodeficiency Virus, see *Intravenous Immune Globulin Use in Patients With*
Human Immunodeficiency Virus, see *Patterns of Primary Care of Patients Infected With*
Human Immunodeficiency Virus Infection in Children Who Received Transfusions in Mexico (Correspondence), Ronald M. Ferdman, Joseph A. Church, Laurene Mascola, Judith K. Sato . . . . . (Nov) 547
Hypercalcemia, see *Intravascular (Angiotropic) Large-Cell Lymphoma ('Malignant Angioendotheliomatosis') With Small-Vessel Pulmonary Vascular Obstruction and*

I

Idiopathic Mediastinitis With Superior Vena Cava Obstruction, Cardiac Tamponade, and Cutaneous Vasculitis, John M. Loeb, Charles M. Lombard . . . . . (Sep) 296
The Ill-Fated Child (Lessons From the Practice), George Zucconi . . . . . (Dec) 664
Immune Globulin Use, see *Intravenous*
'Impairment,' see *Perspectives on*
Incidence of *Chlamydia pneumoniae* Lower Respiratory Tract Infections Among University Students in Northern California, Debra K. Katzman, Ann C. Tipton, Iris F. Litt, Ira M. Friedman, Richard W. Emmons, Julius Schachter . (Aug) 136
Inexpensive, Convenient Adjunct for the Treatment of Diabetes (Correspondence), Gary W. Evans . . . . . (Nov) 549
Interleukin-2 Therapy, see *Cardiomyopathy Associated With High-Dose*
International Health (Editorial), Anvar Velji . . . . . (Sep) 308
Intracranial Hypotension—An Uncommon and Underrecognized Cause of Headache, see *Spontaneous*
Intractable Hiccups as a Presentation of Central Nervous System Sarcoidosis, John P. Connolly, Timothy J. Craig, Ramón M. Sanchez, W. Scott Sageman, Robin E. Osborn. . (Jul) 78
Intravascular (Angiotropic) Large-cell Lymphoma ('Malignant Angioendotheliomatosis') With Small Vessel Pulmonary Vascular Obstruction and Hypercalcemia, Jeffrey L. Curtis, Martha L. Warnock, Douglas J. Conrad, Lisa K. Helfend, Homer A. Boushey . . . . . (Jul) 72
Intravenous Immune Globulin Use in Patients With Human Immunodeficiency Virus-Related Thrombocytopenia Who Need Dental Extraction (Biomedical Science), Mark U. Rarick, Pam Burian, Nelson de Guzman, Byron Espina, Terri Montgomery, Denise Jamin, Alexandra M. Levine . . (Dec) 610
Is Deleting the Digital Rectal Examination a Good Idea?, Mark A. Sutton, Robert P. Gibbons, Roy J. Correa, Jr . . . . (Jul) 43
Correspondence, Pendelton Tompkins . . . . . (Nov) 549
Isoniazid Overdose—Successful Treatment With Pyridoxine and Hemodialysis, Joseph M. Cash, Edward T. Zawada, Jr . . . (Dec) 644

J

Jejunal Brush-Border Folate Hydrolase—A Novel Enzyme (Biomedical Science), Charles H. Halsted . . . . . (Dec) 605

K

[Kidney Stones], see *How We Get Stoned*

L

Large-cell Lymphoma ('Malignant Angioendotheliomatosis') With Small-Vessel Pulmonary Vascular Obstruction and Hypercalcemia, see *Intravascular (Angiotropic)*
Leg Symptoms in Outpatient Veterans, Sylvia K. Oboler, Allan V. Prochazka, Thomas J. Meyer . . . . . (Sep) 256

Lessons From the Practice:

Concerned Patient, Edmund Van Brunt . . . . . (Jul) 88
Desperately Seeking Primary Prevention, Anonymous . . . . . (Sep) 310
Heart and Mind, Marshall H. Chin . . . . . (Nov) 553
The Ill-Fated Child, George Zucconi . . . . . (Dec) 664
My Jogging Partner, Dana Frederick Hoch . . . . . (Nov) 551
My Own Awakening, Robert J. Reiner . . . . . (Dec) 666
Routine Gone Awry, Carl Coppola . . . . . (Aug) 193
Sailor Who Couldn't Play Pool, Paul L. Kingsley . . . . . (Jul) 87

Lethal Leviathan—*Vibrio vulnificus* (Editorial), J. Michael Janda . . . . . (Oct) 421
Leukocyte-Endothelial Interaction, see *Mechanisms and Consequences of*
[Liver Disease], see Vibrio vulnificus—*Hazard on the Half Shell*
Liver Transplantation—Experience With 100 Cases, Jean-Luc Szpakowski, Ken Cox, Paul Nakazato, Waldo Concepcion, Barry Levin, Carlos O. Esquivel . . . . . (Nov) 494
Editorial, Emmet B. Keeffe . . . . . (Nov) 541
Lung Mass and Hemoptysis in a Patient With Tuberculosis (Radiologic Case), Krishnan Padmanabhan, Santi R. Dhar, Kiat Yeo . . . . . (Aug) 181

M

('Malignant Angioendotheliomatosis') With Small-Vessel Pulmonary Vascular Obstruction and Hypercalcemia, see *Intravascular (Angiotropic) Large-Cell Lymphoma*
Managed-Care Plans—Their Future Under National Health Insurance (Commentary), Thomas P. Weil . . . . . (Nov) 533
Massive Splenic Infarction in Doubly Abnormal Heterozygous Sickling Disorders—A New Complication of Acute Splenic Sequestration Syndrome, Roy A. Berry, Elizabeth A. Odumakinde, Jerry P. Lewis. . . . . (Nov) 531
Mechanisms and Consequences of Leukocyte-Endothelial Interaction (Biomedical Science), John M. Harlan, Nicholas B. Vedder, Robert K. Winn, Charles L. Rice . . . . . (Oct) 365
Mediastinal Widening Following Endotracheal Intubation and Gastric Lavage, see *Acute*
Mediastinitis With Superior Vena Cava Obstruction, Cardiac Tamponade, and Cutaneous Vasculitis, see *Idiopathic*
Medicaid, see *Obstetric Care,*
Medicaid, see *Participation of Colorado Pediatricians and Family Physicians in*
Medical Education, Training, and Health Care Services in the Republic of Singapore (Commentary), Chin Hin Chew . . . (Aug) 186
Medical Opinion—A State Medical Association's Experience, see *Perils of Providing*
Medical School, see *Student Perceptions of Mistreatment and Harassment During*
[Medical Students], see *Preceptorships in the 21st Century—The Return of the Apprentice*
Medical Student Section (Editorial), Valentina N. Chen, Robert W. P. Cutler . . . . . (Oct) 421
Medical Tourists (Correspondence), David Bishai . . . . . (Oct) 429
Reply, Fred Wurlitzer . . . . . (Oct) 429
Medicare Assignment Program, see *Redwood*

Medicine and Society:

Obstetric Care, Medicaid, and Family Physicians—How Policy Changes Affect Physicians' Attitudes, Thomas S. Nesbitt, Jeffrey L. Tanji, Joseph E. Scherger, Norman B. Kahn . . . (Dec) 653
Participation of Colorado Pediatricians and Family Physicians in the Medicaid Program, Stephen Berman, Stephanie Wasserman, Susan Grimm . . . . . (Dec) 649

Memoirs of an Amnesiac—Two Years With Brain Cancer, or The Outer Space of Living With Brain Tumors, Alexandra Dane Dor-Ner . . . . . (Nov) 555
Menace of Alcohol (Correspondence), Eben Alexander, Jr . . . (Oct) 430
Reply, Kenneth W. Kizer . . . . . (Oct) 430
Metastasis-Induced Acute Pancreatitis, Shaun S. J. Hung, Bach Ardalan . . . . . (Aug) 176
Metastatic Cancer, see *Numb Chin in*
Mexico, see *Human Immunodeficiency Virus Infection in Children Who Received Transfusions in*
Minority Populations in the United States, see *Health Status of*
Molecular Genetics of Retinitis Pigmentosa (Conferences and Reviews), Moderator: Debora B. Farber; Discussants: John R. Heckenlively, Robert S. Sparkes, J. Bronwyn Bateman . . . . . (Oct) 388
Editorial, Richard G. Weleber, William H. Murphey . . . . . (Oct) 423

Molecular Mechanisms of Cancer (Conferences and Reviews), Moderator: H. Phillip Koeffler; Discussants: Frank McCormick, Christopher Denny ..... (Nov) 505
Editorial, Eric H. Radany ..... (Nov) 544
Motorcycle Accidents, see *Helmet Use Improves Outcomes After*
Motor-Vehicle Accident, see *3-Year-Old Boy With Neck Pain After*
Mouse Joint—Another Manifestation of an Occupational Epidemic?, Lee A. Norman ..... (Oct) 413
My Jogging Partner (Lessons From the Practice), Dana Frederick Hoch ..... (Nov) 551
Myocarditis, see *Aspergillar*
My Own Awakening (Lessons From the Practice), Robert J. Reiner ..... (Dec) 666

N

National Health Insurance, see *Managed-Care Plans—Their Future Under*
Neck Pain After Motor-Vehicle Accident, see *3-Year-Old Boy With*
Neurology, see *Epitomes*
Niacin Therapy in Hospital, see *Fulminant Hepatic Failure Following Low-Dose Sustained-Release*
Nonsteroidal Anti-inflammatory Drugs—Proposed Guidelines for Monitoring Toxicity, Thomas M. Bush, Tammi L. Shlotzhauer, Kent Imai ..... (Jul) 39
The Numb Chin in Metastatic Cancer, Cheryl P. Harris, J. Richard Baringer ..... (Nov) 528

O

Obstetric Care, Medicaid, and Family Physicians—How Policy Changes Affect Physicians' Attitudes (Medicine and Society), Thomas S. Nesbitt, Jeffrey L. Tanji, Joseph E. Scherger, Norman B. Kahn ..... (Dec) 653
Obstetric Care at Teaching and Nonteaching Hospitals, see *Charges for*
Occupational Epidemic?, see *Mouse Joint—Another Manifestation of an*
Oral Contraceptive Use, see *Hepatocellular Carcinoma Coexisting With Hepatic Adenoma—Incidental Discovery After Long-Term*
Orthopedics, see *Epitomes*
Osteoporosis, see *Understanding*
Ovarian Cancer With Medical Therapy, see *Resolution of Bowel Obstruction Due to Newly Diagnosed Inoperable Advanced*

P

Painful Subacute Thyroiditis in Hawaii (Conferences and Reviews), Robert A. Nordyke, Fred I. Gilbert, Jr, Chris Lew ..... (Jul) 61
Editorial, Monte A. Greer ..... (Jul) 83
Pancreatitis, see *Metastasis-Induced Acute*
Participation of Colorado Pediatricians and Family Physicians in the Medicaid Program (Medicine and Society), Stephen Berman, Stephanie Wasserman, Susan Grimm ..... (Dec) 649
Partnerships for Improving Border Health (Commentary), Elena O. Nightingale, Magda G. Peck ..... (Sep) 303
Editorial, Linda Hawes Clever ..... (Sep) 306
Patterns of Primary Care of Patients Infected With Human Immunodeficiency Virus, Marjorie D. Wenrich, Paul G. Ramsey ..... (Oct) 380
Penetrating Extremity Trauma, see *Angiographic Yield in*
Perils of Providing Medical Opinion—A State Medical Association's Experience (Commentary), Hibbard E. Williams, Linda R. Ramsey ..... (Aug) 183
Perspectives on 'Impairment' (Correspondence), Sheldon L. Wagner ..... (Oct) 430
Physician, Heal Thy Planet (Commentary), William B. Stewart ..... (Nov) 538
Physicians and Animal Experimentation (Editorial), Thomas A. Raffin ..... (Sep) 307
Physicians and the Human Immunodeficiency Virus (Editorial), Paul A. Volberding ..... (Nov) 540
Planet, see *Physician, Heal Thy*
Polyarteritis Nodosa, see *Bilateral Spontaneous Renal Hemorrhage Due to*

Poems:

Aneurysm, Stephen Lyons ..... (Dec) 620
Case Histories—Oncology, Anne Kavanaugh ..... (Oct) 369
Doctor's Wife, Constance Pultz ..... (Nov) 537
Ear, Freya Manfred ..... (Dec) 615
Eleventh Hour, Constance Pultz ..... (Oct) 432
In a Convalescent Hospital, Janet Lewis ..... (Aug) 194
In Praise of Old Men's Pee, Elaine Starkman ..... (Oct) 432
Inserting a Chest Tube Without Anesthesia, Michele Wyrebek ..... (Dec) 662
Older Brother, Julia Kasdorf ..... (Nov) 539
On an Old Woman Dying, Janet Lewis ..... (Jul) 38
Out in the Trenches, Elizabeth Spencer Smith ..... (Jul) 82
Sick Child, Stephanie Pershing Buehler ..... (Nov) 504
The Toronto Dogs, Carlos A. Schaffenburg ..... (Sep) 312
To Pronounce the Dead, Antoinette Reed ..... (Jul) 46

Poisoning, see *Ciguatera Fish*
Positive Preemployment Urine Drug Screen Caused by Foreign-Manufactured Vitamin Formulation (Correspondence), M. Joseph Fedoruk, Loretta Lee ..... (Dec) 663
Practical Approach to Acid-Base Disorders (Conferences and Reviews), Discussant: Richard J. Haber ..... (Aug) 146
Preceptorships in the 21st Century—The Return of the Apprentice (Editorial), F. Marian Bishop, Neal A. Whitman ..... (Oct) 426
Preemployment Urine Drug Screen Caused by Foreign-Manufactured Vitamin Formulation, see *Positive*
Pregnancy, see *Screening for Hepatitis B During*
Primary Care Physicians, see *Smoking Cessation Attitudes, Practices, and Policies Among California*
Primary Ciliary Dyskinesia (Conferences and Reviews), Laurie Le Mauviel ..... (Sep) 280
Psychiatry, see *Epitomes*
Psychosis, see *Severe Thyrotoxicosis Presenting as Acute*
Public Interest in Human Growth Hormone Therapy (Correspondence), Paul S. Salva, George E. Bacon ..... (Oct) 428
Public Perceptions of Health Care Problems—An Analysis From Arizona, Bradford L. Kirkman-Liff ..... (Sep) 269
Pulmonary Vascular Obstruction and Hypercalcemia, see *Intravascular (Angiotropic) Large-Cell Lymphoma ('Malignant Angioendotheliomatosis') With Small-Vessel*
Pyridoxine, see *Isoniazid Overdose: Successful Treatment With*

Radiologic Cases:

Acute Mediastinal Widening Following Endotracheal Intubation and Gastric Lavage, Krishnan Padmanabhan, Hari Gadde, Samir Vora ..... (Oct) 419
Lung Mass and Hemoptysis in a Patient With Tuberculosis, Krishnan Padmanabhan, Santi R. Dhar, Kiat Yeo ..... (Aug) 181
3-Year-Old Boy With Neck Pain After Motor-Vehicle Accident, Wazhma Aslamy, Kelvin Danielson, Samuel J. Hessel, Jonathan M. Levy ..... (Sep) 301
2-Year-Old Girl With Seizures and Fever, Alice N. Karolewski, Virginia C. Poirier ..... (Dec) 647

Recruiting Physicians to Rural Practice—Suggestions for Success, Katherine Riley, Wayne Myers, Ronald Schneeweiss ..... (Nov) 500
Rectal Examination a Good Idea?, see *Is Deleting*
Redwood Medicare Assignment Program (Correspondence), Herbert Notkin ..... (Jul) 86
Rehabilitation Potential, see *Evaluating Cancer Patients for*
Renal Calculi, see *Causes and Prevention of Calcium-containing*
Renal Hemorrhage, see *Bilateral Spontaneous*
[Residents], see *Preceptorships in the 21st Century—The Return of the Apprentice*
Resolution of Bowel Obstruction Due to Newly Diagnosed Inoperable Advanced Ovarian Cancer With Medical Therapy, Thomas P. Drakes ..... (Jul) 76
Retinitis Pigmentosa, see *Molecular Genetics of*
Routine Gone Awry (Lessons From the Practice), Carl Coppola ..... (Aug) 193
Rural Practice—see *Recruiting Physicians to*

S

Sailor Who Couldn't Play Pool (Lessons From the Practice),

Paul L. Kingsley . . . . . (Jul) 87
Salicylate Toxicity, see *Fatal*
Sarcoidosis, see *Intractable Hiccups as a Presentation of Central Nervous System*
Sarcoidosis of the Breast, Central Nervous System, and Exocrine Glands in a Patient With Sicca Symptoms, Kenneth H. Fye, Ripley H. Hunter . . . . . (Dec) 642
Screening for Hepatitis B During Pregnancy—Awareness of Current Recommendations Among Washington Hospitals, Thomas R. Eng, Mary L. Borges, Vivian K. Harlin, John M. Kobayashi . . . . . (Dec) 613
Severe Thyrotoxicosis Presenting as Acute Psychosis, Timothy G. Caudill, Claude K. Lardinois . . . . . (Sep) 292
Sicca Symptoms, see *Sarcoidosis of the Breast, Central Nervous System, and Exocrine Glands in a Patient With*
Sickling Disorders, see *Massive Splenic Infarction in Doubly Abnormal Heterozygous*
Singapore, see *Medical Education, Training, and Health Care Services in*
Smoking Cessation Attitudes, Practices, and Policies Among California Primary Care Physicians (Correspondence), Russell L. Young, Catherine Crooks, John P. Elder, Erin Kenney, Dileep G. Bal, Michael Johnson . . . . . (Nov) 548

Special Article:

Memoirs of an Amnesiac—Two Years With Brain Cancer, or The Outer Space of Living With Brain Tumors, Alexandra Dane Dor-Ner . . . . . (Nov) 555

Splenic Infarction, see *Massive*
Splenic Sequestration Syndrome, see *Massive Splenic Infarction in Doubly Abnormal Heterozygous Sickling Disorders—A New Complication of Acute*
Splenomegaly, see *Clinical Diagnosis of*
Spontaneous Intracranial Hypotension—An Uncommon and Underrecognized Cause of Headache, Michael B. Jacobs, Philip H. Wasserstein . . . . . (Aug) 178
Status Epilepticus—Clinical Features, Pathophysiology, and Treatment (Conferences and Reviews), Craig Watson . . . . . (Dec) 626
Student Perceptions of Mistreatment and Harassment During Medical School—A Survey of Ten United States Schools, DeWitt C. Baldwin, Jr, Steven R. Daugherty, Edward J. Eckenfels . . . . . (Aug) 140
Subacute Thyroiditis (Editorial), Monte A. Greer . . . . . (Jul) 83
Subsalicylate, see *Fatal Salicylate Toxicity From Bismuth*
Superior Mesenteric Artery Thrombosis Associated With Antiphospholipid Syndrome, Maurice E. Hamilton . . . . . (Aug) 174
Superior Vena Cava Obstruction, Cardiac Tamponade, and Cutaneous Vasculitis, see *Idiopathic Mediastinitis With*
Surgery, General, see *Epitomes*

T

Tabasco Products Can Be Hazardous to Your Health, see *WARNING—Inhaling*
Taxes and Abortion (Correspondence), Laura Hammons . . . . (Dec) 663
Teething as a Cause of Death—A Historical Review (Commentary), Harry L. Gibbons, C. Kent Hebdon . . . . . (Dec) 658
There's a Long, Long Trail A-winding (Editorial) . . . . . (Nov) 540
3-Year-Old Boy With Neck Pain After Motor-Vehicle Accident (Radiologic Case), Wazhma Aslamy, Kelvin Danielson, Samuel J. Hessel, Jonathan M. Levy . . . . . (Sep) 301
Thrombocytopenia, see *Intravenous Immune Globulin Use in Patients With Human Immunodeficiency Virus-Related*
Thrombosis, see *Home Treatment of Calf Deep Venous*
Thombosis Associated With Antiphospholipid Syndrome, see *Superior Mesenteric Artery*
Thyroiditis, see *Subacute*
Thyroiditis in Hawaii, see *Painful Subacute*
Thyrotoxicosis Presenting as Acute Psychosis, see *Severe*
Tort Reform Works (Correspondence), Joseph D. Sabella . . . . (Oct) 428
Toxic Exposure to Betamix (Correspondence), Marc Tunzi . . (Nov) 548
Toxic Shock Syndrome, see *Cisplatin Therapy-Associated Recurrent*
Training, and Health Care Services in the Republic of Singapore, see *Medical Education, Training, and*
Transfusions in Mexico, see *Human Immunodeficiency Virus Infection in Children Who Received*
Transplantation, see *Liver*
Trauma, see *Angiographic Yield in Penetrating Extremity*
Trial and Tribulation of Egerton Yorrick Davis (Commentary), Gerard N. Burrow . . . . . (Jul) 80
Tuberculosis, see *Lung Mass and Hemoptysis in a Patient With*
Tuberculosis Presenting as Fever of Unknown Origin, see *Gastric*
Tumor Malignancy, see *Autocrine Growth Factors and Solid*
Two Medical Worlds—Separate and Unequal (Editorial), Woodrow A. Myers, Jr . . . . . (Jul) 83
2-Year-Old Girl With Seizures and Fever (Radiologic Case), Alice N. Karolewski, Virginia C. Poirier . . . . . (Dec) 647

U

Understanding Autocrine Growth Regulation (Editorial), Robert J. Coffey, John A. Barnard . . . . . (Aug) 189
Understanding Osteoporosis (Conferences and Reviews), Robert Marcus . . . . . (Jul) 53
United States, see *Health Status of Minority Populations in*
Upper Gastrointestinal Tract Hemorrhage (Conferences and Reviews), Discussant: Loren Laine . . . . . (Sep) 274
Urine Drug Screen Caused by Foreign-Manufactured Vitamin Formulation, see *Positive Preemployment*
Urology, see *Epitomes*

V

Value of Defiance (Correspondence), Howard M. Grindlinger (Oct) 431
Vasculitis, see *Idiopathic Mediastinitis With Superior Vena Cava Obstruction, Cardiac Tamponade, and Cutaneous*
Venous Thrombosis, see *Home Treatment of Calf Deep*
Vibrio vulnificus—Hazard on the Half Shell (Conferences and Reviews), Kristi L. Koenig, Juergen Mueller, Theodore Rose . . . . . (Oct) 400
Editorial, J. Michael Janda . . . . . (Oct) 421
Violence—Risk Factors and Outcomes, see *Domestic*
Vitamin, see *Dietary Folate*
Vitamin Formulation, see *Positive Preemployment Urine Drug Screen Caused by Foreign-Manufactured*

W

WARNING—Inhaling Tabasco Products Can Be Hazardous to Your Health (Correspondence), Haya R. Rubin, Albert W. Wu, Sean Tunis . . . . . (Nov) 550
Warning Labels on Food, see *Do We Need*
Washington Hospitals, see *Screening for Hepatitis B During Pregnancy—Awareness of Current Recommendations Among*
[Women Physicians], see *There's a Long, Long Trail A-winding*

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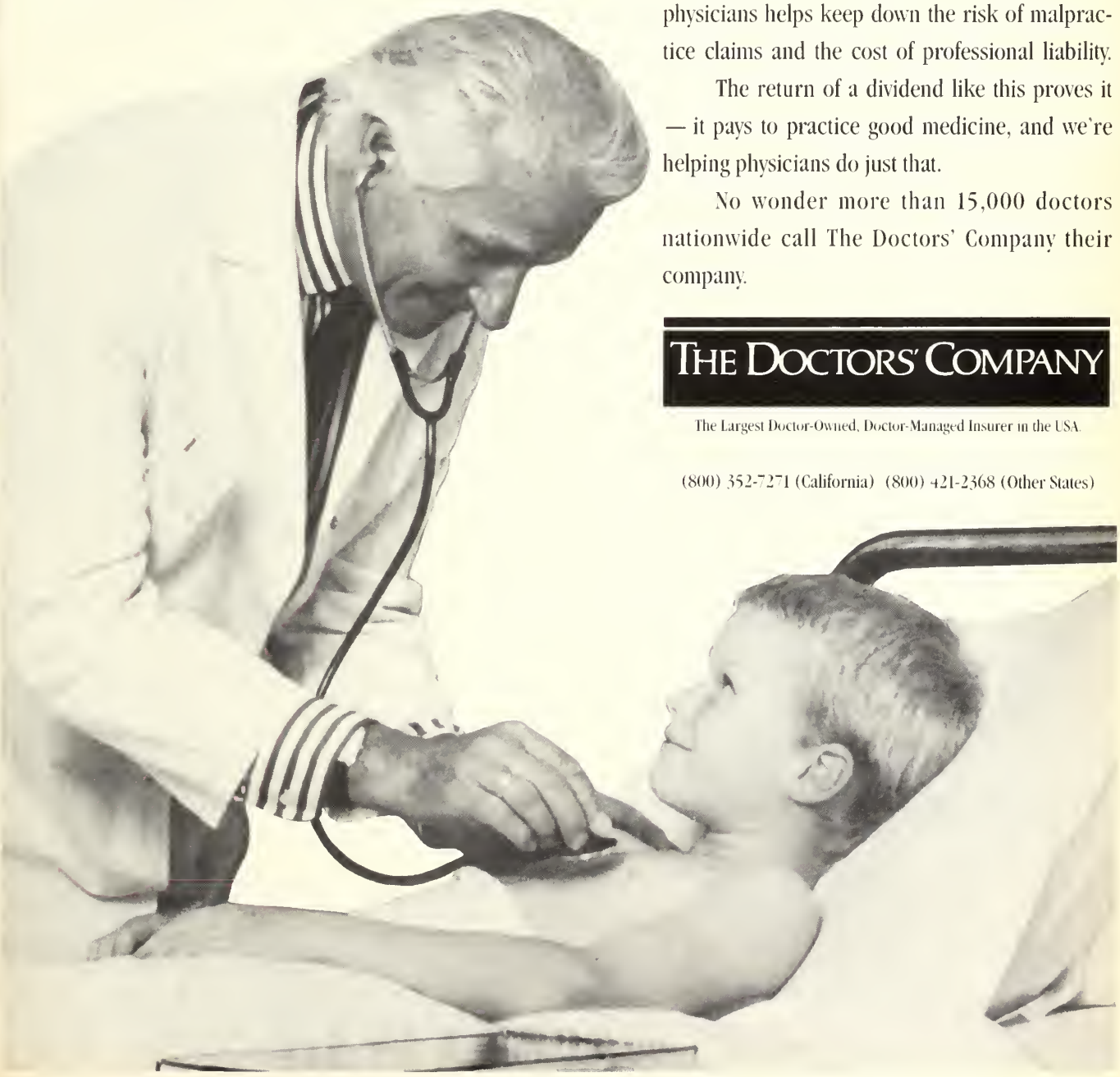


(Continued from Page 602)

March 22-27—**MRI Workshop in Hawaii: 1992.** Queens Medical Center at Kea Lani Hotel, Wailea, Hawaii. Sun-Fri. 37 hrs. $595. Contact: Susan Block, Queens Medical Ctr, 1301 Punchbowl St, Honolulu, HI 96813. (808) 547-4544.

April 5-10—**General Radiology Review Course.** UCLA at Miramar Sheraton Hotel, Santa Monica. Sun-Fri. 40 hrs. $425. Contact: UCLA.

April 19-24—**Residents Radiology Review Course.** UCSD at Hotel del Coronado, San Diego. Sun-Fri. 39 hrs. $470. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

April 25—**Interventional Radiology.** UCSD at Hotel del Coronado, San Diego. Sat. 8 hrs. $125. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

May 4-8—**MRI: A State of the Art Clinical Review.** Stanford University Medical Center at Ritz-Carlton, San Francisco. Mon-Fri. 23.5 hrs. $540. Contact: UCSD.

May 8-10—**Advanced Seminars in Diagnostic Imaging.** UCSD at Ritz-Carlton, Laguna Niguel. Fri-Sun. 15 hrs. $400. Contact: UCSD.

May 21-24—**Doppler and Duplex Imaging.** UCSD at Le Meridien Hotel, San Diego. Thurs-Sun. 21.5 hrs. Contact: UCSD.

REHABILITATIVE/THERAPEUTIC

March 5-7—**Rehabilitation: Science, Technology, Quality and Costs—Present and Future.** Scripps Memorial Hospital at La Jolla Marriott. 18.5 hrs. $395. Contact: Meeting Management, 5665 Oberlin Dr, Ste 110, San Diego 92121. (619) 453-6222.

SLEEP MEDICINE

January 30-31—**New Horizons in Sleep Disorders Medicine.** California Thoracic Society at Doubletree Resort, Palm Springs. Thurs-Fri. Contact: California Thoracic Society, 202 Fashion Ln, #219, Tustin 92680. (714) 730-1944.

April 3-4—**Pharmacotherapeutics in Clinical Sleep Medicine.** Scripps Clinic and Research Foundation at La Jolla. Fri-Sat. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

SURGERY

January-May 1992—**Temporal Bone Surgical Dissection Courses.** House Ear Institute at Los Angeles. 6 days each. 53 hrs. $1100. Contact: Antonio De la Cruz, House Ear Institute, 2100 W 3rd St, Los Angeles 90057. (213) 483-4431, ext 7079.

January 17-18—**What's New in General Surgery.** UCD at Radisson Hotel, Sacramento. Fri-Sat. 16 hrs. $295. Contact: UCD.

February 8-11—**International Symposium on Hair Replacement Surgery.** American Academy of Facial Plastic and Reconstructive Surgery at Century City J W Marriott, Los Angeles. Sat-Tues. Contact: Sharon Clawson, (213) 278-8823.

February 9-14—**15th Annual San Diego Postgraduate Assembly in Surgery.** UCSD at Hotel del Coronado, San Diego. Sun-Fri. Contact: UCSD.

February 12-14—**2nd International Lung Transplant Symposium: Update 1992.** Cedars-Sinai Medical Center at Ritz-Carlton, Laguna Niguel. Wed-Fri. 6.5 hrs. $500. Contact: Carolyn Lavitt, Continuing Education, 8700 Beverly Blvd, Los Angeles 90048. (213) 855-5547.

March 18-21—**Surgical Challenges in the Head and Neck: A Dissection Course Emphasizing Contemporary Strategies.** UCSD at Basic Science Bldg, La Jolla. Wed-Sat. Contact: UCSD.

March 19-22—**42nd Annual Surgical Forum.** Society of Graduate Surgeons at Beverly Hilton, Beverly Hills. Thurs-Sun. Contact: SGS, 5820 Wilshire Blvd, Ste 500, Los Angeles 90036. (213) 937-5514.

April 2-4—**12th Annual Meeting and Scientific Sessions of the International Society for Heart Transplantation.** UCSD at San Diego Marriott. Thurs-Sat. Contact: UCSD.

GENERAL/MULTIDISCIPLINARY

December 24-30—**Advances in Medicine.** Hawaii Medical Association at Royal Lahaina Resort, Kaanapali Beach. Thurs-Wed. 16 hrs. $475. Contact: Symposium Maui, PO Box 833, Makawao, Maui, HI 96768. (808) 878-6757.

January 25-27 and March 1-2—**Lactation Educator Training Programs.** UCLA at Loma Linda. 22.5 hrs. $725. Contact: UCLA.

February 24-28—**Physician Heal Thyself.** UCSD at San Diego Princess Resort. Mon-Fri. Contact: UCSD.

February 28-29—**Nutrition: A Key Partner in the Treatment of Frequently Encountered Medical Problems.** UCD at Walnut Creek. Fri-Sat. Contact: UCD.

March 12-13—**Dimensions of Caring 1992: Enhancing Quality of Life in Palliative Care.** Scripps Clinic and Research Foundation at Omni Hotel, San Diego. Thurs-Fri. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

April 2-4—**Medicine Today.** UCSD at Price Center. Thurs-Sat. Contact: UCSD.

April 9-13—**Lactation Educator Training Programs.** UCLA at Westwood. 22.5 hrs. $725. Contact: UCLA.

COLORADO

This listing of continuing medical education programs in Colorado is compiled by the Denver Medical Society. To list CME programs here, please send information at least two months in advance to: Mr Robert L. Kennedy, Denver Medical Society, 1850 Williams Street, Denver, CO 80218; or telephone (303) 377-1850.

Brochures, course information, and registration forms are available from the contact person or organization.

December 21-April 11, 1992 (17 Weekly Meetings)—**Second Annual Vail Computers in Medicine Conference.** Rose Medical Center at L' Ostello Lodge, Vail. One week. Contact: David R. Scott, (800) 525-5810.

January 9-11—**Twenty-Seventh Annual Conference on Occupational Medicine & Colorado/AMA Guides to Evaluation of Permanent Impairment Course.** The Rocky Mountain Academy of Occupational Medicine and Colorado State Association of Occupational Health Nurses at Hyatt Regency Tech Center, Denver. Thurs-Sat. Contact: Douglas Scott, MD, (303) 782-9129.

January 25-February 1—**Reconstructive Surgery of the Hip and Knee.** University of Colorado School of Medicine at Snowmass Conference Center, Snowmass Village. One week. Contact: Joann Bauer, (303) 270-5195 or (800) 882-9153.

January 25-February 1—**15th Annual Infectious Diseases in Clinical Practice.** UCSF at Beaver Run Resort and Conference Center, Breckenridge. Sat-Sat. 24 hrs. Contact: UCSF.

February 8-15—**Seventeenth Annual Vail Psychiatry Conference.** Rose Medical Center and University of Colorado School of Medicine at Lion Square Lodge, Vail. One week. Contact: David R. Scott, (800) 525-5810.

February 8-15—**Sixth Annual Duke Symposium on Dermatologic and Rheumatic Diseases.** Duke University Medical Center at Marriott Mark Resort, Vail. One week. Contact: Symposium Coordinator, Duke University, (800) 457-1125.

February 8-15—**Fourteenth Annual Vail Emergency Medicine Conference.** Rose Medical Center and University of Colorado School of Medicine at Marriott Mark Resort, Vail. One week. Contact: David R. Scott, (800) 525-5810.

February 10-14—**Family Practice Review.** University of Colorado School of Medicine, Denver. Mon-Fri. Contact: Joann Bauer, (303) 270-5195 or (800) 882-9153.

February 14-16—**Advanced Laparoscopy for the General Surgeon.** Rose Medical Center and University of Colorado School of Medicine at Loew's Giorgio Hotel and University of Colorado Health Sciences Center, Denver. Fri-Sun. Contact: David R. Scott, (800) 525-5810.

February 15-22—**Eighteenth Annual Vail Obstetrics and Gynecology Conference.** Rose Medical Center and University of Colorado School of Medicine at Marriott Mark Resort, Vail. One week. Contact: David R. Scott, (800) 525-5810.

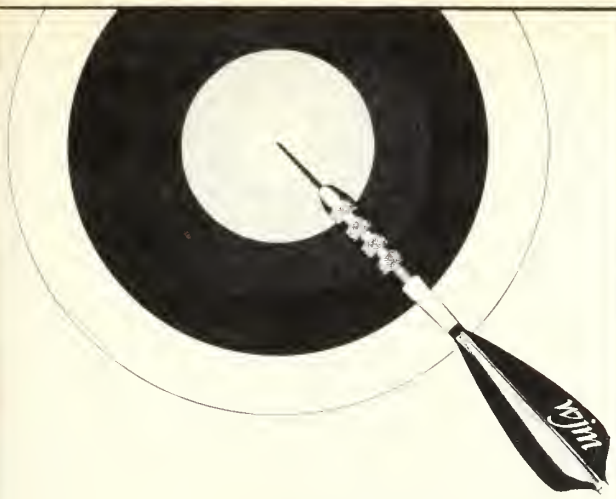
February 15-22—**Seventeenth Annual Vail Internal Medicine Conference.** Rose Medical Center and University of Colorado School of Medicine at Lion Square Lodge, Vail. One week. Contact: David R. Scott, (800) 525-5810.

February 22-29—**Seventeenth Annual Vail General and Vascular Surgery Conference.** Rose Medical Center and University of Colorado School of Medicine at Marriott Mark Resort, Vail. One week. Contact: David R. Scott, (800) 525-5810.

February 22-29—**Neurology for the Primary Care Physician.** Rose Medical Center and University of Colorado School of Medicine at The Antlers at Vail. One week. Contact: David R. Scott, (800) 525-5810.

February 28-March 2—**Principles of Anesthesia Technology.** University of Colorado School of Medicine at Marriott Mark Resort, Vail. Fri-Mon. Contact: Joann Bauer, (303) 270-5195 or (800) 882-9153.

(Continued on Page 682)



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References:

1. A. Morales et al., New England Journal of Medicine: 1221. November 12, 1981.
2. Goodman, Gilman — The Pharmacological basis of Therapeutics 6th ed., p. 176-188. McMillan December Rev. 1/85.
3. Weekly Urological Clinical letter, 27:2, July 4, 1983.
4. A. Morales et al., The Journal of Urology 128: 45-47, 1982.

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(Continued from Page 680)

February 29-March 7—**Colorado Review of Anesthesia.** University of Colorado School of Medicine at Marriott Mark Resort, Vail. One week. Contact: Joann Bauer, (303) 270-5195 or (800) 882-9153.

February 29-March 7—**Horizons in Surgery.** University of Colorado School of Medicine at Beaver Run Resort, Breckenridge. One week. Contact: Joann Bauer, (303) 270-5195 or (800) 882-9153.

February 29-March 7—**Third Annual Vail Infectious Disease Conference.** Rose Medical Center and University of Colorado School of Medicine at The Antlers at Vail. One week. Contact: David R. Scott, (800) 525-5810.

February 29-March 7—**Fourteenth Annual Vail Pediatrics Conference.** Rose Medical Center and University of Colorado School of Medicine at Marriott Mark Resort, Vail. One week. Contact: David R. Scott, (800) 525-5810.

March 7-14—**Seventeenth Annual Vail Primary Care Conference.** Rose Medical Center and University of Colorado School of Medicine at Marriott Mark Resort, Vail. One week. Contact: David R. Scott, (800) 525-5810.

March 7-14—**"Minding the Body, Mending the Mind": Influencing Health and Healing.** Rose Medical Center and University of Colorado School of Medicine at The Antlers at Vail. One week. Contact: David R. Scott, (800) 525-5810.

March 7-14—**Fifteenth Annual Vail Cancer Treatment Conference.** Rose Medical Center and University of Colorado School of Medicine at The Antlers at Vail. One week. Contact: David R. Scott, (800) 525-5810.

March 14-21—**Fifteenth Annual Vail Urology Conference.** Rose Medical Center and University of Colorado School of Medicine at Marriott Mark Resort, Vail. One week. Contact: David R. Scott, (800) 525-5810.

March 14-21—**Fourteenth Annual Vail Sports Medicine Conference.** Rose Medical Center and University of Colorado School of Medicine at Marriott Mark Resort, Vail. One week. Contact: David R. Scott, (800) 525-5810.

March 16-19—**Nineteenth Annual Neonatal and Infant Respiratory Symposium.** Ohio State University Hospitals at Marriott Mark Resort, Vail. Mon-Thurs. Contact: Arlene Rogers, Ohio University Hospitals, (614) 293-8487.

March 21-28—**Headache and Facial Pain Conference.** Rose Medical Center and University of Colorado School of Medicine at The Antlers at Vail. One week. Contact: David R. Scott, (800) 525-5810.

March 21-28—**Fourth Annual Colorado Geriatrics Overview/Board Review.** University of Colorado School of Medicine at Iron Horse Resort, Winter Park. One week. Contact: Joann Bauer, (303) 270-5195 or (800) 882-9153.

First Wednesday of Each Month—**Various Topics in Neurology.** Sponsored by the Colorado Society of Clinical Neurologists. Contact: Colorado Society of Neurologists, (303) 449-3566.

CONTACT INFORMATION

U of Colo—Contact: University of Colorado School of Medicine, Office of Continuing Medical Education, 4200 E 9th Ave, Denver, CO. (303) 270-5195.

IDAHO

February 21-23—**33rd Annual Medical Winter Clinics—Wilderness and Travel Medicine.** Ada County Medical Society at Shore Lodge, McCall. Fri-Sun. 9 hrs. Cat. 1. $100 for Idaho Medical Association members; $150, nonmembers. Contact: Judy Barningham, Ada County Medical Society, PO Box 2668, Boise 83701. (208) 336-2930.

NEW MEXICO

Information, requests for accreditation, and items to be listed should be sent to the chair of the CME Committee, New Mexico Medical Society, 7770 Jefferson, Suite 400, Albuquerque, NM 87109, at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 828-0237.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

February 28-29—**20th Annual New Mexico Thoracic Society Lung Disease Conference.** El Dorado Hotel, Santa Fe. Contact: Billie Dytzel, 216 Truman, NE, Albuquerque 87108. (505) 265-0732.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. Accredited institutions wishing to list AMA Category 1 CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, UT 84102; or phone (801) 355-5290. For information on CME accreditation, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution.

MEDICAL GRAND ROUNDS

Each Wed—8:00-9:00 a.m. Alternating between University of Utah Medical Center and VA Medical Center, Salt Lake City. Contact: William D. Odell, MD, PhD, Professor and Chairman, Dept of Internal Medicine, Univ of Utah, (801) 581-7606.

January 8-11—**Arthritic Hip, Knee and Shoulder** (Sponsor: UUSM). Wed-Sat. Snowbird. Contact: UUSM.

January 15-18—**Craniofacial/Oculoplastic Surgery** (Sponsor: UUSM). Wed-Sat. Snowbird. Contact: UUSM.

January 26-30—**Pediatric Critical Care Colloquium** (Sponsor: UUSM). Sun-Thurs. Snowbird. Contact: UUSM.

February 3-7—**Surgical Pathology** (Sponsor: UUSM). Mon-Fri. Park City. Contact: L. Larsen, (801) 581-5854.

February 9-14—**Interventional Radiology** (Sponsor: UUSM). Sun-Fri. Park City. Contact: Judy Gallegos, (801) 581-8188.

February 10-14—**Eleventh Annual Dermatology Seminar** (Sponsor: UUSM). Mon-Fri. Park City. Contact: Rosalie Lammle, (801) 581-8664.

February 14-15—**1992 Winter Ski Meeting** (Sponsor: Utah Ophthalmological Society). Fri-Sat. Prospector Square Hotel, Park City. Contact: Mark Fotheringham, (801) 355-7477.

SPONSORS OF COURSES—ABBREVIATIONS

AHA:	American Heart Association, Utah Affiliate, 645 E 400 South, Salt Lake City 84102. (801) 322-5601.
CH:	Castleview Hospital (formerly Carbon Hospital), RFD 2, Box 46, Price 84501. (801) 637-4800.
HCH:	Holy Cross Hospital, 1045 E First South, Salt Lake City 84102. (801) 350-4744.
ITS:	Intermountain Thoracic Society, 1616 S 11th East, Salt Lake City 84105. (801) 484-4456.
LDSH:	LDS Hospital, 8th Ave and "C" St, Salt Lake City 84143. (801) 321-1100.
LRH:	Logan Regional Hospital, 1400 N 5th East, Logan 84321. (801) 752-2050.
MDH:	McKay-Dee Hospital Center, 3939 Harrison Blvd, Ogden 84409. (801) 399-4141.
MVH:	Mountain View Hospital, 1000 E Highway 6, Payson 84651. (801) 465-9201.
144:	144th Evacuation Hospital, PO Box 8000, Salt Lake City 84108. (801) 524-3924.
OSS:	Ogden Surgical Society, PO Box 9311, Ogden 84409.
PVH:	Pioneer Valley Hospital, 3460 S 4155 West, West Valley City 84120. (801) 968-9061.
UOS:	Utah Ophthalmological Society, 540 E 500 South, Salt Lake City 84102. (801) 355-7477.
USH:	Utah State Hospital, PO Box 270, Provo 84603-0270. (801) 373-4400.
UUSM:	University of Utah School of Medicine, Office of Continuing Medical Education, 50 N Medical Dr, Salt Lake City 84132. (801) 581-8664.
VAMC:	Veterans Administration Medical Center, 500 Foothill Dr, Salt Lake City 84148. (801) 582-1565.
VVMC:	Valley View Medical Center, 595 S 75 East, Cedar City 84720. (801) 586-6587.
WRI:	Western Rehabilitation Institute, 8074 S 1300 East, Sandy 84094. (801) 561-3400.

(Continued on Page 684)

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CONTINUING MEDICAL EDUCATION

(Continued from Page 682)

February 14-18—**Syncope** (Sponsor: UUSM). Fri-Tues. Olympia Hotel, Park City. Contact: UUSM.

February 15-22—**Update in Clinical Microbiology and Immunology** (Sponsor: UUSM). Sat-Sat. Park City. Contact: Midge Beckman, (801) 581-7480.

February 17-21—**Pediatric Emergency Medicine** (Sponsor: UUSM). Mon-Fri. The Marriott, Salt Lake City. Contact: UUSM.

February 19-24—**Physical Medicine and Rehabilitation Update** (Sponsor: UUSM). Wed-Mon. Radisson Inn, Park City. Contact: UUSM.

February 20-21—**Protecting Your Right to Prescribe** (Sponsor: UUSM). Thur-Fri. University Park Hotel, Salt Lake City. Contact: Sharon Thompsen, (801) 355-7477.

February 23-26—**The 32nd Annual OB/GYN Update** (Sponsor: UUSM). Sun-Wed. Yarrow, Park City. Contact: S. Martin, (801) 581-5501.

February 26-29—**Infertility and Endocrinology Update** (Sponsor: UUSM). Wed-Sat. Yarrow, Park City. Contact: S. Martin, (801) 581-5501.

February 28-Mar 3—**The 36th Anesthesiology Update** (Sponsor: UUSM). Fri-Tue. Snowbird. Contact: V. Larsen, (801) 581-6393.

WASHINGTON

The listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here, please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle, WA 98121; or phone (206) 441-WSMA.

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

January 16—**Law and Medicine Symposium.** Tacoma. Thurs. Contact: PCMS.

January 16-17—**Alzheimers Update.** Seattle. Thurs-Fri. Contact: U/W.

January 24-25—**WTS Chest Conference.** Seattle. Fri-Sat. Contact: Washington Thoracic Society, (206) 441-5100.

January 31—**Vascular Surgery Update for Primary Care Providers.** Seattle. Fri. Contact: VMMC.

February 6-7—**A Day in the Office: Problems in Pediatric Practice 1992.** Seattle. Thurs-Fri. Contact: Group Health, (206) 326-3441.

February 7—**Review of HIV Infections.** Tacoma. Fri. Contact: PCMS.

February 14—**Cancer and the Nervous System.** Seattle. Fri. Contact: VMMC.

February 28—**Office Intervention: Alcohol and Substance Abuse.** Tacoma. Fri. Contact: PCMS.

March 9-13—**Geriatric Board Review.** Seattle. Mon-Fri. Contact: U/W.

March 9-19—**Physical Medicine and Rehabilitation.** Bellevue. Mon-Thurs. Contact: U/W.

March 12-13—**Internal Medicine Review—1992.** Tacoma. Thurs-Fri. Contact: PCMS.

March 20—**Integrated Approach to the Dizzy Patient.** Seattle. Fri. Contact: VMMC.

March 22-25—**Urgent Problems in Primary Care.** Bend, Oregon. Sun-Thurs. Contact: Group Health, (206) 326-3441.

March 25—**Ethics Conference.** Seattle. Wed. Contact: VMMC.

March 23-26—**Death Investigations.** Seattle. Mon-Thurs. Contact: U/W.

March 25-27—**Spirometry Training for Worker Screening.** Seattle. Wed-Fri. Contact: NW Center for Occupational Health and Safety, (206) 543-1069.

March 30-April 3—**Hawaii and CME.** Kauai, Hawaii. Mon-Fri. Contact: PCMS.

April 10—**Recent Developments in Occupational Medicine.** Seattle. Fri. Contact: NW Center for Occupational Health and Safety, (206) 543-1069.

April 10—**Gastro-Esophageal Reflux: A Multi-faceted Disease.** Seattle. Fri. Contact: VMMC.

April 17-18—**Tacoma Surgical Club.** Tacoma. Fri-Sat. Contact: PCMS.

April 24—**Annual Day of Pediatrics.** Tacoma. Fri. Contact: Multicare, (206) 594-1221.

April 24-25—**Diabetes of the Eye.** Seattle. Fri-Sat. Contact: U/W.

April 24-25—**Low-Back Pain.** Seattle. Fri-Sat. Contact: VMMC.

April 30-May 2—**Musculoskeletal Disease.** Seattle. Thurs-Sat. Contact: U/W.

May 8—**Office Procedures.** Tacoma. Fri. Contact: PCMS.

May 13-15—**Fifth Conference on Occupational Hazards to Health Care Workers.** Seattle. Wed-Fri. Contact: NW Center for Occupational Health and Safety, (206) 543-1069.

May 21-22—**Cardiology Conference.** Tacoma. Thurs-Fri. Contact: Multicare, (206) 594-1221.

May 27—**Pesticide Medicine.** Eastern Washington. Wed. Contact: NW Center for Occupational Health and Safety, (206) 543-1069.

May 30—**The Fetal Patient.** Seattle. Sat. Contact: VMMC.

June 22-23—**Advanced Cardiac Life Support.** Tacoma. Mon-Tues. Contact: PCMS.

June 26—**Sports Medicine.** Tacoma. Fri. Contact: Multicare, (206) 594-1221.

September 9-12—**Washington State Medical Association Annual Meeting.** Jantzen Beach, Oregon. Thurs-Sun. Contact: WSMA.

September 23-24—**Critical Care.** Tacoma. Thurs-Fri. Contact: Multicare, (206) 594-1221. ◆

COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Avenue, Seattle, WA 98104 (206) 223-5953.

PCMS CME—Contact: Mrs Maxine Bailey, Executive Director, College of Medical Education, 705 South Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON)—Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

WSMA—Washington State Medical Association, Continuing Medical Education, 2033 Sixth Ave, Suite 900, Seattle, WA 98121. (206) 441-9762.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, PO Box 900, Seattle, WA 98111. (206) 223-6898.

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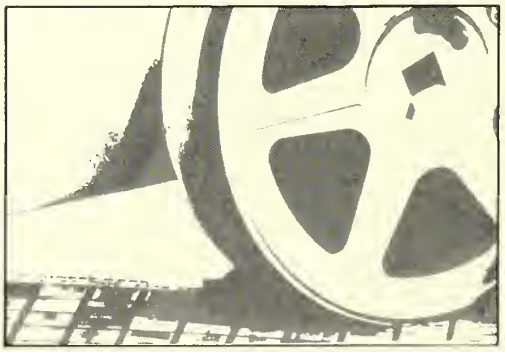

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Our readership represents all specialties of medicine. We wish to receive and publish manuscripts that are valid, important, lively, well-written, and succinct. They should be of interest to a broad range of busy practitioners, students, researchers, and scholars who have a clinical orientation. The purpose of a paper or letter may be to alert, review, discuss—above all, to teach. Titles should be short and intriguing. Avoid jargon, the overuse of abbreviations and acronyms, sexist language, redundancies, or expendable words and phrases (see *AMA Manual of Style*, 8th Edition).

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Manuscripts should be sent to the Editor, Linda Hawes Clever, MD, *The Western Journal of Medicine*, 221 Main Street, San Francisco, California 94105. Manuscripts must be original, not previously published, and not under consideration by another publication. If preliminary data were included in another presentation or publication, that should be noted in the cover letter and a copy of that publication should be included.

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Journal Articles

Abbreviations of journal titles should conform to those used in *Index Medicus*. List up to six authors; for seven or more, use et al after listing the first three.

1. Jones JS, Anderson HW Jr, Johnson DW, et al: The athletic heart revisited—Sudden death of a 28-year-old athlete. JAMA 1978; 292:444-456
2. Berman SM, Shah B, Wyle FA, Dacosta-Iyer M, McRae DM: Disseminated *Pneumocystis carinii* in a patient receiving aerosolized pentamidine prophylaxis. West J Med 1990; 153:82-86

Books

3. Berne EJ: Role playing in therapy, chap 2, Principles of Group Therapy. New York, NY, Oxford University Press, 1966, pp 35-51 (author of book is same as author of chapter)
4. Munsung JD: The role of drugs, chap 2, *In* Brest AN, Mayer JD (Eds): Hypertension—Vol 3, Therapy, 2nd Ed. Chicago, Ill, Year Book Medical Publishers, 1961, pp 456-479 (authors of book differ from chapter author)

Correspondence

5. Shusterman D: Espresso maker's wrist (Correspondence). West J Med 1990; 152:721-722

Government Publications

6. The Health Consequences of Smoking—Cardiovascular Disease: A Report of the Surgeon General. Washington, DC, US Dept of Health and Human Services publication No. (PHS) 84-50204, 1983
7. Centers for Disease Control: Update: Acquired immunodeficiency syndrome—United States. MMWR 1987; 36:522-526

Proceedings

8. O'Connell M: A Controlled Trial of Regional Intra-arterial FUDR Versus Systemic 5FU for the Treatment of Metastatic Colorectal Cancer Confined to the Liver. Presented at the annual meeting of the American Society of Clinical Oncology, San Francisco, December 1989

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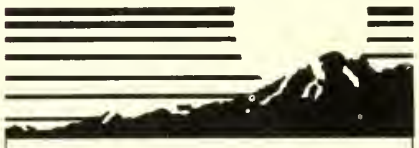

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(Continued on Page 687)

(Continued from Page 686)

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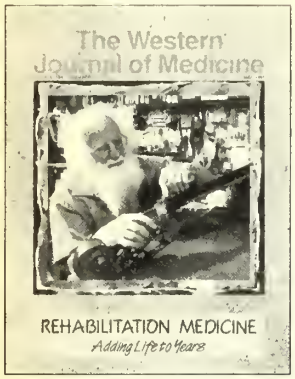

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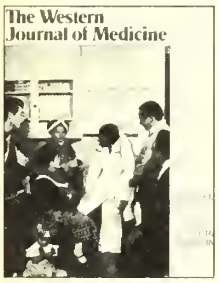

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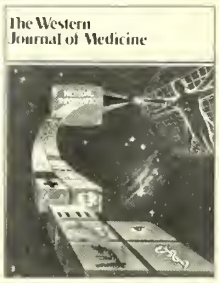

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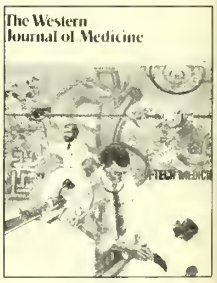

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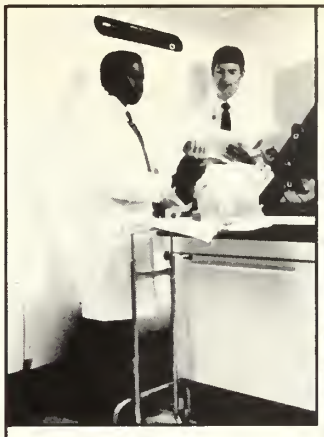

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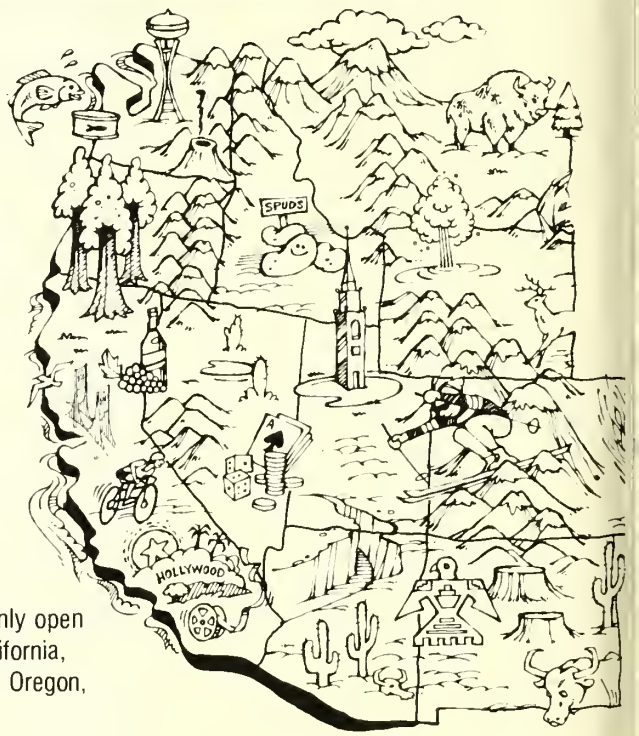

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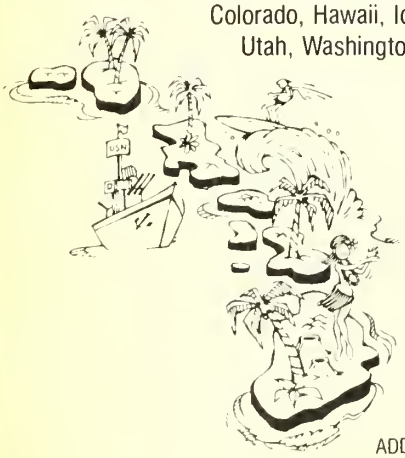

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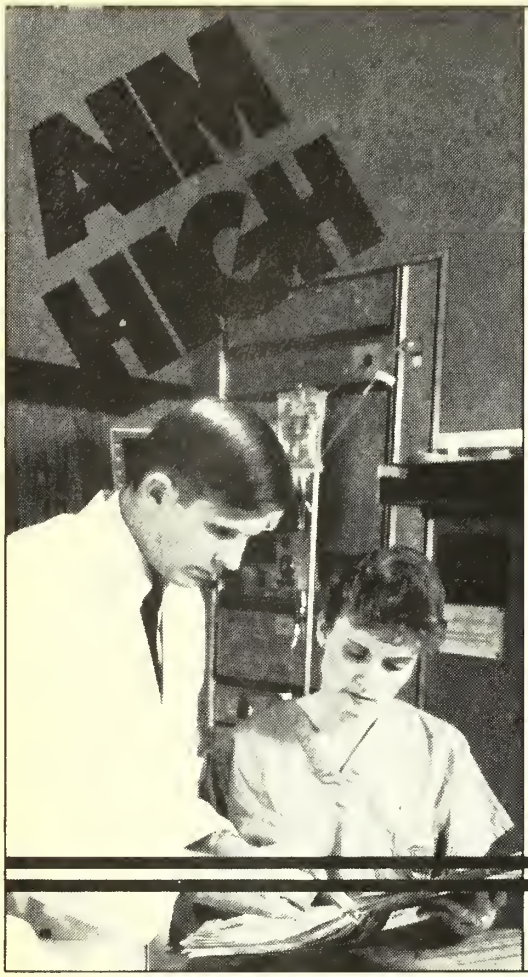
(Continued on Page 694)



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Montana Medical Association—2012 11th Ave, Suite 12, Helena 59601. (406) 443-4000. Annual Meeting: 1992, date and location to be announced.

Nevada State Medical Association—3660 Baker Lane, Reno 89502. (702) 825-6788. Annual Meeting: April 23-26, 1992, Sheraton Grand Torrey Pines, La Jolla, California.

New Mexico Medical Society—7770 Jefferson, Suite 400, Albuquerque 87109. (505) 828-0237. Annual Meeting: May 14-16, 1992, Albuquerque.

Oregon Medical Association—5210 SW Corbett Ave, Portland 97201. (503) 226-1555. Annual Meeting (House of Delegates only): 1992, date and location to be announced.

Utah Medical Association—540 E Fifth South, Salt Lake City 84102. (801) 355-7477. September 16-19, 1992, University Park Hotel, Salt Lake City.

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Wyoming Medical Society—PO Drawer 4009, Cheyenne 82003-4009. (307) 635-2424. Annual Meeting: June 11-13, 1992, Jackson Lake Lodge, Moran.

ADVERTISING INDEX

AMERICAN COLLEGE OF PHYSICIANS
Annual Session 599

BRISTOL-MYERS SQUIBB COMPANY
BuSpar 583, 584
Provachal 579

CALIFORNIA MEDICAL ASSOCIATION
Annual Session 601

CIGNA HEALTHPLAN 689, 691

CLASSIFIED ADVERTISING 686, 687, 689, 690, 691, 693, 694, 695, 696, 697

COASTAL GOVERNMENT SERVICES INC 689

DOCTORS' COMPANY 679

ELI LILLY & COMPANY
Humulin 589, 683

FHP HEALTH CARE 687

FOREST PHARMACEUTICALS INC.
AeroBid . . . . . 2nd cover, 577, 578

GROUP HEALTH COOPERATIVE 603

HOFFMANN LA ROCHE LABORATORIES
Librax 590, 591
Valium . . . . . 3rd and 4th covers

INSURANCE CORPORATION OF AMERICA 597

KAISER PERMANENTE 693

MERCK SHARP & DOHME
Mevacor 593, 594, 595, 596

PALISADES PHARMACEUTICALS INC.
Yocon 681

G.D. SEARLE & COMPANY
Calan SR 587

SMITHKLINE BEECHAM PHARMACEUTICALS
Tagamet 603, 604

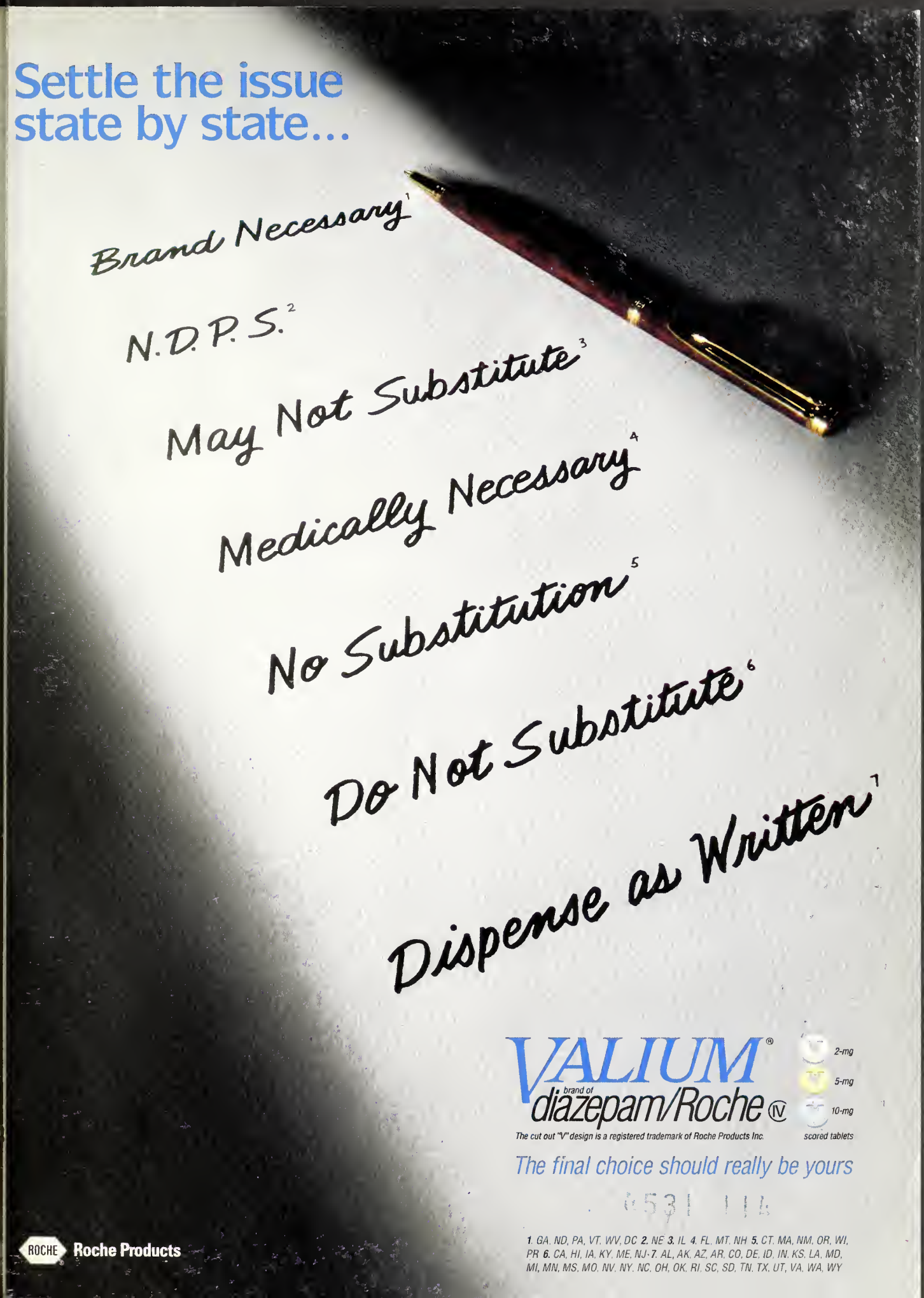
UNIVERSITY MICROFILM 684

UNIVERSITY SOUTHERN CALIFORNIA
University Hospital 581

US AIR FORCE 694

VOICE CARE SYMPOSIUM 603

THE WESTERN JOURNAL OF MEDICINE
Medical Student Writing Award 692
Special Issues 688
Subscription 578, 681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